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Circadian rhythms, magnesium status and clinical disorders: possible pathophysiological and therapeutical importance of various types of light therapy and of treatment through light deprivation, melatonin and their mimicking agents

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Various links between the biological clock and magnesium status are highlighted: balanced magnesium status could enhance the effects of photoperiod on supra chiasmatic nuclei (SCN) and on pineal secretion (melatonin = MT). Reversely darkness therapy may potentiate the effects of magnesium therapy.
Conventional bright light therapy appears as a speedy and efficient antidepressant medication useful for the treatment of various types of depression and of non migrainous headaches. Althought the decrease in melatonin production ('MT) seems accessory the increase in serotonegy and perhaps in reactive oxygen species (;ROS) constitute the main mechanisms of action. Further research should determine the place of chromatotherapy.
Conversely, although the increased production of MT constitutes the best marker of darkness, it is only an accessory mechanism of its action. The psycholeptic effects of darkness, similarly to those of magnesium, rely on direct membraneous and oxidant actions, neural mediated effects (stimulation of inhibitory neuromodulators such as GABA and taurine (TA) and on antogonism of neuroactive gases. Darkness therapy *per se*, partial substitutive therapy with MT and with their mimicking agents (Mg, LTP, TA) apply to all the chronopathological disorders, with decreased production of MT. But the chronopathological forms of Mg depletion appear as selective indications. Further research should determine their importance in the physiopathology of various forms of neural hyperexcitability such as insomnia, migraine, chronic fatigue syndrome, fibromyalgia, some forms of asthma..., whose treatments could therefore be improved.

KEY WORDS: *Chronopathology, supra chiasmatic nuclei, pineal gland, melatonin, taurine, magnesium, tryptophan, nervous hyper excitability, insomnia, migraine, chronic fatigue syndrome, fibromyalgia.*

Magnesium and regulation of the K-CL contrasporter

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In exocrine pancreas, Singh et al[1] have shown that agonist-evoked acinar secretion is associated to cell magnesium exit and decrease in cytosolic magnesium contents. However, acinar cell secretion is triggered by increases in cytosolic calcium. Therefore, the physiological role of agoniste-evoked cell magnesium decrease is unclear. In rat thymocytes, 150 mM KCI evokes a very important magnesium efflux, about 90 times higher as the physiological magnesium efflux catallyzed by the Na-Mg exchanger. Cells remained viable (trypan blue test) and membrane integrity was shown by the absence of increase in sodium permeability. K^+ -induced magnesium efflux exhibited the following properties: a) it required the presence of external chloride; b) it was fully blocked by DIOA, a selective KCl-cotransporter inhibitor (IC_{50} = 35 μm), and c) it was associated to a progressive increase in cell volume via the DIOA-ssnsitive K-Cl cotransporter. Such cell swelling seems to play a causal role, because: a) hypertonic media (+ 400 mM sucrose) abolished K^+ -induced magensium efflux, and b) hypotonic Ringer media (205 mOsm) increased both, cell volume and magnesium efflux (from a basal value of 0.35 ± 0.03 mmoles/l.cells/20 min up to 1.44 ± 0.24 mmoles/l.cells/20 min), even in the presence of DIOA. Therefore, high potassium activates inward K-Cl cotransport, thus inducing cell swelling, which in turn activates magnesium efflux and further activates K-Cl cotransport. Such explosive phenomenon suggested that a new magnesium transport mechanism is involved in the transduction signal of K-Cl cotransporter activation. In this respect, it is important to mention that, in salivary acinus, acethylocholine induces cell swelling, followed by cell shrinkage[2].

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KEY WORDS: *Magnesium, K-Cl cotransport, volume regulation, DIOA.*

Eukaryotic magnesium transporters

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We are characterizing the first known eukaryotic Mg2+ transporters, named Alr1p and Mrs2p/Lpe10p. These proteins are distant relatives of the bacterial CorA Mg2+ transporter, characterized by two adjacent transmembrane domains and a short sequence motif in the connecting peptide. Alr1p is known to occur in lower eukaryotes only and has been localized in the plasma membrane of yeast cells. Mrs2p and Lpe10p are two related proteins in the yeast mitochondrial inner membrane. The human genome encodes a single Mrs2/Lpe10 homologue, which has been located in the mitochondria, whereas the Arabidopsis encodes ten homologues of which some appear to be mitochondrial.
Overexpression of either the yeast MRS2/LPE10 genes or the Alr1 gene results in a significant increase of Mg2+ whereas the disruption of one or the other gene causes a twofold reduction of Mg2+ in mitochondria or in whole cells, respectively. Other metal ions appeared not to be affected. With the aid of the fluorescence probe mag-fura 2, we observed changes of the free Mg2+ in cells and isolated mitochondria dependent on external Mg2+ concentrations. Mg2+ influxes were drastically reduced when the MRS2 or the ALR1 gene was knocked out. These data are consistent with the notion that Mrs2p and Alr1p act as a Mg2+ transporters in the mitochondrial membrane and in the plasma membrane, respectively.
Analyzing physiological effects of changes in Mg2+ concentrations in mrs2o yeast mutants we noted pronunced effects on the splicing of RNAs containing group II introns. As a further effect we observed reduced assembly and/or stability of respiratory complexes of the inner mitochondrial membrane. These results indicate that some cellular functions are particulary sensitive to changes of Mg2+ concentrations.

Magnesium and arterial hypertension

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Numerous experimental, epidemiological and clinical findings have point out a possible role for magnesium deficiency in the development of human arterial hypertension.
Small reduction in free intracellular and/or extracellular magnesium concentration increases vascular contractility and reactivity indicating the importance of this ion in blood pressure regulation and supporting its possible role in the pathogenesis of human hypertension.
There are epidemiological findings showing a significant protective effect of magnesium intake from drinking water on the risk of hypertension and indicating that magnesium content in tap water is inversely related to the risk of death from hypertension.
Bodily magnesium deficiency, disclosed by magnesium loading test, is usually detectable among patient with essential arterial hypertension and become particulary evident in salt-sensitive hypertensives.
Although these data support a pathological role for magnesium deficiency in the etiology and the pathogenesis of hypertension, the available clinical studies give more conflicting and less convincing results.
The majority of the observational studies indicate a negative association between dietary magnesium intake and blood pressure levels and, generally, a small but significant blood pressure reduction after increasing dietary magnesium content. However, the therapeutic value for oral magnesium supplementation in the treatment of human essential hypertension is still uncertain and debated, with some clinical studies indicating favorable effects of various magnesium salts on blood pressure levels and others no effect at all.
Diuretics are one of the most common treatment for essential hypertension and the majority of the oral formulations classically used as antihypertensive pharmacotherapy (such as hydrochlorothiazide or chlorthalidone 25 mg) are magnesiuretic. Prolonged treatment with diuretically active formulations of these drugs may conduce to magnesium deficit and loss of the antihypertensive efficacy of the treatment itself. In this setting, the restoration of bodily magnesium deficiency is highly effective in lowering blood pressure.
In conclusion, despite a growing body of evidences indicating a physiological and pathophysiological role of magnesium in blood pressure regulation and in the development of hypertension, the potential antihypertensive therapeutic effect of treatment with magnesium in the management of essential hypertension is still debated. At the moment, a routine evaluation of magnesium status in patients at risk of depletion of this cation and a dietary or pharmacological magnesium supplementation when a deficit is detected, are recommendable measure in patients with essential hypertension.

Magnesium in patients with heart failure

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Total serum magnesium concentration is low in a netoworthy percentage of patients who present congestive (C) heart failure (HF) and normal renal function. Hypomagnesaemia has been found to be associated with a reduction in survival in these patients.
Excess magnesiuresis caused by common diuretics (loop and/or thiazide-type drugs) is habitually the main causative factor of hypomagneseaemia in CHF patients. The loop diuretic furosemide increases magnesiuresis by decreasing the reabsorption of filtered magnesium at the loop of Henle and at the nephronal proximal tubule. The loop diuretic torasemide is devoid of significant proximal action, and its effect on serum magnesium concentration is generally bening. Renal magnesium loss would be favoured by the increase in plasma aldosterone that occurs as a consequence of some of the renal actions of diuretics and/or as part of the HF syndrome. The antialdosterone diuretic spironolactone causes only mild renal retention of magnesium in individuals with high plasma aldosterone concentration. Patients who also present type 1 or type 2 diabetes, alcoholics and subjects who consume high amounts of caffeine are at higher risk of developing magnesium deficit from excess magnesiuresis.

Magnesium deficit in CHF appears to result in myocardial calcium overload. This change may cause or concur to the occurrence of serious cardiac arrhythmias. Magnesium deficit also attenuates or impedes the antiarrhythmic effect of potassium replenishment in patients with severe hypokalaemia. Although magnesium deficit could theoretically aggravate HF by impairing the production of energy for cardiac contraction, hypomagnesaemia appears to reduce life expectancy in CHF patients solely through an elevation in the risk of perilous cardiac arrhythmias and sudden death.

Cyclosporin and tacrolimus, which are used a immunosuppressants in patients with transplanted hearts, increase magnesiuresis strikingly and conduce to hypomagnesaemia and to a decrease in myocardial magnesium in most patients. Thus heart transplant recipients treated with these drugs should receive magnesium supplements.

The progress of CHF conveys a progressive deterioration of renal function. Consequently, magnesiuresis decreases and serum magnesium concentration tends to increase and may surpass its upper normal limit. Hypermagnesaemia constitutes a marker of poor prognosis in advance HF.

The purport of magnesium deficit for cardiac contraction in the failing heart should be researched comprehensively. The responses of urine and serum magnesium to potential new drugs for HF, such a neutral endopeptidase inhibitors, vasopeptidase inhibitors and anti-endothelin drugs, and to new immunosuppressants such as rapamycin (sirolimus), gusperimus and mycophenolate mofetil merit specific investigative endeavours.

Mg^{2+} binding and its structural

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Evidence is accumulating on the interaction of Mg^{2+} as hexahydrated cation with DNA domains forming architectural $[Mg(H_2O_6)]^{2+}$DNA asssemblies as well as $[Mg(H_2O)_5]^{2+}$DNA coordination complexes. In the first case the «free» hexahydrated magnesium is linked to DNA through electrostatic charges to the phosphate negative groups (PO_2) of the bakbone and hydrogen bounded through the water hydrogens to electronegative sites, and in the second case the coordinated penta -/or tetra hydrated magnesium is linked to DNA through a covatent coordinate -bond to electronegative oxygens (predominantly) or nitrogen sites, electrostatically to two negatively charged nucleotides (PO_2^-) groups and also hydrogen bonded to several electronegative sites. However, when the concentration of Magnesium is increased we may have also other phenomena of aggregation and the formation of binary and ternary nuclear complexes. Structural models of these complexes are discussed and compared for their precise architecture and assembly.

Regulation of protein phosphorylation in brain and liver mitochondria by magnesium and calcium with emphasis on subunit c of ATP synthase

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We have at the 6th Euromag presented data showing modulation of subunit c phosphorylation by Mg^{2+} and Ca^{2+} in mitochondria affecting the ATPase and ATP synthase activities. Effect of various Mg concentration in range from 5mM, 1mM, 500 mkM and 100 mkM in Ca-EGTA buffer at 10^{-7}M Ca and 10^{-6}M Ca^{2+} on the incorporation of [γ^{32}P]ATP into protein of brain and liver mitochondria has been studied. Na [γ^{32}P]ATP (50 and 500 μM) were used in the control. The phosphoproteins with kDa's of 3.5 (subunit c), 17, 40-43, 55-60 and above 60 with additional phosphobands appearing in range of 8-10 kDa in the presence of 1 μM Ca^{2+} have been observed in the brain rat mitochondria. The level phosphorylation was decreased at 500 and 100 μM Mg^{2+}. Subunit c phosphorylation is more higher at the μM NaATP. In rat liver mitochondria protein phosphorylation spectr is differ. It was found phosphorylation of 50, 40-45, 30 and 3,5 kDa. Additonal band of 8-10 kDa has been observed in the presence of 1μM Ca or in the presence 50 μM NaATP at any Ca concentration. The phosphopeptide of 8-10 kDa is not identified yet. The nature inhibitor of OS-ATPase, obtained by Pulmann and Monro (IF1), has similar molecular mass. Taking into consideration data on inhibiting of ATPase activity of Esherihia coli by TNI (inhibitor subunit of troponin) that possesses ability to be phosphorylated, one can suggests that probably inhibitor of F_0F_1-ATPase-IF1 also might be phosphorylated and observed 8-10 kDa is phosphorylated form of IF1. We have shown earlier that subunit c dephosphorylation is related to permeability transition pore opening and calcineurin was suggested to be involved into its dephosphorylation. Since the phosphatase is metalloenzyme, containing Zn^{2+} we investigated effect of Zn^{2+} on the mPTP opening. At 5μM Zn^{2+} was shown the decreasing of the subunit c phosphorylation takes place, correlated with opening mPTP. Zn induced opening of PTP is prevented by CsA. Obtained data indicate involving dephosphorylation of subunit c (ATP synthase/hydrolase) related to mPTP.

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Magnesium and the influence of DNA structure

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Magnesium ions participate in almost all anabolic and catabolic functions. There is evidence, both epidemiological and experimenta supporting the hypothesis that magnesium deficiency causes leu-

kemia and other cancers. The role of magnesium in carcinogenesis is not clear. Durlach et al[1,2] reported that magnesium deficiency sometimes induces anticancer and some times carcinogenic effects. They suggest that the carcinogenic action of magnesium is linked to amino-acid metabolism and immune systems. Oilier investigation have shown that magnesium deficient diet indues an increase of tumor necrosis factor a (TNF-a) in rat serurm[3] Using ^{60}Co-gamma rays we have produced superoxide anions in order to study the role of magnesium ions on 5'-guanosine monophosphate. It was found that upon irradiation in the presence of oxygen the magnesium ions are released from the 5'guanosme monophosphate complex, leading to the magnesium-oxygen products, according to the reactions.

$$2O_2^- \rightarrow O_2^{2-} + O_2$$
$$Mg^{2+} + O_2 \rightarrow \{Mg\text{-}O_2\}$$

These findings are in agreement with results obtained by Masumoto et al[4], which show that superoxido anion transported through anion channels into cells decrease the intracellular free magnesium ion concentration by direct interaction, and that this reaction is independent on pH. It was also found that the presence of magnesium ions protects the nucleotide from OH radicals, since they prevent the opening of imidazole ring. The importance of magnesium tons is to stabilize the structure in tRNA and DNA by binding to specific sites, depending on the hydration state of the metal.

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Non-specific and specific immune response alterations in magnesium deficiency: experimental data

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Mg plays an essential role in fundamental cellular reactions and it was recognized that Mg deficiency exerts deleterious consequences on the immune system.The aim of our studies was to determine alterations of the immune response due to Mg deficiency and to precise mechanisms at the origin of these alterations. Experimental Mg deficiency in rats induces after few days characteristic inflammatory syndrome including increase in plasma levels of IL-6 and several acute phase proteins. The phagocytic cells from deficient rats present characteristics of activated cells (increase in respiratory burst and phagocytic activity) and their responses to immune stress is exacerbated. On the opposite, increasing concentrations of extracellular Mg reduce the response of rat and human phagocytic cells to the immune stress. This point out on the potential beneficial anti-inflammatory role of pharmacological concentration of Mg. The proposed mechanism for the activation of phagocytic cells involves an abnormal Ca handling induce by extracellular Mg depression. Moreover, results in Mg-deficient rats fed a normal or low-Ca diet suggest that the proinflammatory effect of Mg deficiency is the consequence of a reduced extracellular Mg^{2+}/Ca^{2+} antagonism resulting in an increased intracellular free Ca^{2+} concentration. The low concentrations of Mg, which lead to the inflammation, could be related to several pathological consequences observed during this deficiency i.e. exacerbated response to the immune stress, hyperlipemia and cardio-vascular damages. Several alterations of specific immunity were also recorded in Mg-deficient animals i.e. accelerated thymus involution, reduced specific IgA production by intestinal mucosa. In summary, it appears from these experimental data that Mg deficiency in early stages induces an acute phase response with activation of non-specific immune defence system. If prolonged, this deficiency could contribute to exhausting phagocytic cell activity. It also appears that Mg deficiency rapidly affects immune cells involved in the specific immunity.

Magnesium and exercise: an update

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Prolonged intensive exercise exposes subjects to magnesium depletion, which can aggravate the consequences of a frequent marginal deficiency. Magnesium depletion and deficiency play a role in the pathophysiology of physical exercise.
Individuals practising exercise that are prone to magnesium deficit could be more susceptible to free radicals mediated injury, which could contribute to increase the tissue damage resulting from exercise.
There is evidence that immunoregulation during and after intense physical exercise is influenced by transient or manifest deficiencies in several nutrients including magnesium.

Magnesium: physiological actions and genetic disorders of distal tubule reabsorption

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Magnesium, an essential element for life, is the third most abundant mineral of bone after calcium and phosphate. The remainder of the body's magnesium is chiefly within the cells; so, it is, after potassium the most copious intracellular cation. In the blood, most of magnesium is found in the form of a free ion, Mg^{2+}, or complexed

both to inorganic (sulfate, phosphate, carbonate) and organic (citrate, oxalate, gluconate, palmitate, ATP) molecules. Intracellular magnesium performs a plenty of physiological functions, beings its major job to stabilize structures such as ATP, DNA and RNA. Magnesium also plays an important role in protein synthesis, glycolisis and mitochondrial oxidate metabolism; thus, magnesium is essential for energy metabolism. In mammalians, magnesium homeostasis mainly occurs via renal function, which comprises glomerular filtrarion and tubule transport. Glomerular filterability: 70%-80% of total plasma magnesium; the proximal tubule reabosrbs < 15%; most of the filtered Mg is reabsorbed along the thick ascending limb (TAL) of the Henle's loop; and 5%-10% of the filtered Mg along the distal tubule. At last, 5%-10% of the filtered Mg is definitively excreted in the urine. Distal tubule Mg absorption is transcellular, whereas Mg transport within the TAL occurs across a paracellular pathway (through tight junctions), and precisely, has been identified a new human gene protein, calledparacellin-1 (PCLN-1) or claudin 16, mutations in which cause renal magnesium wasting with hypomagnesemia, hipokalemia and hipercalciuria. But another inherited disorder characterized by hypomagnesemia, hypokalemia and hypocalciuria, called Gitelman's syndrome, has also been recently described.

KEY WORDS: *hypomagnesemia, paracellin-1, TAL, distal tubule, Gitelman's syndrome.*

Hypotonic shock activates a cell magnesium extrusion mechanism in rat acinar gland salivary cells

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In salivary and other exocrine glands, calcium ion plays the key role in the signal transduction mechanism of secretagogue-induced exocytosis. Stimulation of acinar cell secretion by acethylcholine is associated to other events such a important cell shrinkage[1] and a rapid and transient magnesium efflux[2]. However, the role of magnesium in cell secretion remained elusive for years, due among others to the lack of reliable methods to measure intracellular magnesium. Here we applicated a previously developped Mg Fluo 4-technique[3] to isolated submandibular acinar cells, in order to investigate the role of magnesium in secretory cell function.
Methods Isotonic medium (mM) = NaCl 145, KCl 5, $MgCl_2$ 1, $CaCl_2$ l, MOPS-Tris 10 (pH 7.4), glucose 10 with carboten (95% O^2 + 5% CO^2).
Hypotonic media = NaCl 72.5, KCl 5, $MgCl_2$ l, $CaCl_2$ l, MOPS-Tris 10 (pH 7.4), glucose 10 with carbogen (95% O^2 + 5% CO^2).
Results: Hypotonic shock (160 mOsm) induced an important and transient decrease in cytosolic free magnesium content. Free magnesium content were reduced to 50% in 15 sec, recovering to 90% of the original levels in about 1 min. This was associated to an important and very rapid magnesium efflux.
Magnesium signal induced by hypotonic shock had the following characteristics: a) it wa more important to that induced by acethylcholine; b) it was fully blocked by increasing extracellular magnesium up to 40 mM, and c) it was also inhibited by removing carbogen for 15 min.
Hypotonic shock induced a very important cell swelling, but not potassium efflux or RVD (regulatory volume decrease).
In clonclusion, hypotonic shock activates a cell magnesium extrusion mechanism in rat acinar gland salivary cells. However, this was not associated to the triggering of any RVD mechanism.

Biochemical links between diphosphonates and HMG-CoA reductase inhibitors: does the mevalonate pathway play a crucial role in the regulation of magnesium influx?

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HMG-Co reductase inhibitors and diphosphonates share direct effects on the mevalonate pathway and thus influence cholesterol wynthesis. In a previous report HMG-CoA reductase inhibitors have been shown to increase erythrocyte Mg influx and erythrocyte Mg content. Epidemiological studies have further raised an issue on the potential for HMG-CoA reductase inhibitors to benefit osteoporotic patients. As diphosphonates, which are first-line antiresorptive agents to prevend and treat osteoporosis, also interfere with the mevalonate pathway, we were interested to examine the effects of diphosphonates on erythrocyte and renal Ca and Mg handling. The role Mg deficiency appears to play in osteoporosis further substantiated this study. Retrospective data from the DONMAG cohort suggest similarities between HMG-CoA reductase inhibitors and alendronate on Mg handling. The present work further reports on 3 prospective cases. The results that are obtained add to the case for Mg in the management and prevention of osteoporosis and support a direct effect of both diphosphonates and HMG-CoA reductase inhibitors on erythrocyte Mg influx, possibly due to the inhibition of the mevalonate pathway resulting in changes in the membrane Na-K-ATPase activity.

Circulating MG levels in type 1 diabetic patients with and without gastric motility disorders

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Nearly 1/3 of type 1 diabetic patients (T1DM) present with Mg depletion essentially due to increased urinary losses. Hypochorhydria as a consequence of associated gastric autoimmunity does not seem to play on essential role in the Mg status of T1DM. It is however possible that delayed gastric emptying frequently present in T1DM as a consequence of hyperglyucemia or autonomic dysfunction could interfere with intestinal Mg availability. Gastric emptying was measured in 42 T1DM with wellrecognised isotopic techniques (^{13}C octanoic acid for solids and ^{13}C glycine for liquids). Delayed solids emptying was observed in 17 patients who also had a significantly nihger HbA1c (8.4% sd 0.9 versus 7.5 h sd 1, p = 0.005). Serum Mg (1.78 mg/dl sd 0.16 versus 1.8 mg/dl sd 0.18) and erythrocyte Mg (5.81 mg/dl sd 0.75 versus 5.71 mg/dl sd 0.61) were however identical in both groups. Delayed liquid emptying existed in 15 patients who showed also a trend to increased preva-

lence of autonomic neuropathy (p = 0.07). Although plasma Mg levels were again identical in both groups, erythrocyte Mg was higher (6.25 mg/dl sd 1 versus 5.6 mg/dl sd 0.46, p = 0.052) in the patients with delayed liquid emptying. Lower daily urinary losses (60.4 mg versus 90.3 mg) in the presence of an identical metabolic control suggest a higher body retention perhaps related to a more progressive delayed gastro-intestinal absorption. Dynamic studies with Mg-isotopes could give a better insight in this phenomenon.

Statins do not alter the magnesium status in type 1 insulindependent diabetic patients

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Serum total magnesium (S-Mg) decreases during treatment with fibrates and statins in patients with type 2 diabetes. The objetive of this study was to evaluate if the magnesium status is also affected by hypolipidemic drug treatment in type 1 diabetic patients (T1DM). Indeed a survey in 243 T1DM, erythrocyte-Mg (RBC-Mg) was lower than 5.5 mg/dl in 30% of the patients with a net preponderance in the female gender. 45 patients (31 men, 14 women) were treated with hypolipidemic drugs for more han 1 year. The prevalence of low RBC-Mg was significantly lower (Fisher Exact test: p = 0.0049) in this group as compared to the non treated group (n = 198). This observation was more pronunced in the female population (p = 0.0174) but no difference was observed between fibrate or statine treatment. In order to evaluate prospectively the effect of statins on S-Mg and RBC-Mg 22 T1 DM (19 men, 3 women) were followed during 6 months receiving 20 mg atorvastatine daily. The metabolic control (HbA1c at the start: 7.98% sd 1.1) remained stable after 3 and 6 months (Anova: p = 0.6). Total cholesterol (Anova: p = 0.0001), LDL-cholesterol (Anova: p = 0.0001) and triglycerides (Anova: =0.005) decreased significantly but S-Mg (1.8 mg/dl sd 0.16 versus 1.84 sd 0.16) and RBC-Mg (5.88 mg/dl sd 0.63 versus 5.895 sd 0.7) remained unchanged. In conclusion, it can be stated that in stable T1DM treatment with statins does not influence parameters of Mg status. No significant correlation could be found with any of the lipid levels.

Low magnesium intake is an aetiological factor in the development of osteoporosis in the rat

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Introduction: In postmenopausal osteoporotics it was shown that an oral magnesium (Mg) administration for 2 years caused a significant increase in bone density (BD) in most patients. No other medication for osteoporosis was given (Magnes Res 1993; 6:155-63). The question was raised whether in experimental animals given a Mg deficient food for a year a lower BD could be found compared to controls given a Mg-standard chow.
Methods: We followed the effect on BD in female Sprague-Dawley rats given either an 200 ppm MgO chow (A) or a 2000 ppm MgO containing food (B) for 12 months together with an otherwise identical diet (Sniff, Germany, Soest). Eight randomly selected animals received food A and eight animals food B. After one year the animals were sacrificed and the BD values of a standardized area in the 3rd-5th lumbar vertebral region and of the femural bones were measured BD was assessed using the same method as that used for patients: DEXA dual energy X-ray absorptiometry (Prodgy, LUNAR Europe, Brussels, Belgium). The use of a standardization technique (Biomaterials, 1992; 13:462-6) allowed for a precision of 12.5% CV. The mean of three repeated measuremets was used. Values were compared using independent t-tests.
Results: The mean BD in L3 to L5 region in animals given food A was: 0.253 (0.014) and in animal given food B 0.290 [0.044, p = 0.031 (1 -tail)]. The mean BD in the femural region in group A was: 0.275 (0.037), and in group B 0.315 (0.044, p = 0.047 (1-tail)].
Conclusion: Using a technique, which is the golden standard for diagnosing osteoporosis in man, BD was found to be significantly lower in rats after on year under a Mg-deficient food compared to animals given the standard Mg-food. This demostrates that low Mg intake constitutes an aetiological factor in the development of osteoporosis.

From epidemiological evidence to clinical trials: a comprehensive research project to address the role of magnesium in bone health in Switzerland

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Osteoporosis has been claimed as one of the six major health hazards to be considered a priority for biomedical research in Switzerland. The role Mg deficiency may play in osteoporosis remains unsettled. The case for longterm oral Mg supplementation has been received some support from open trials. Applying recently reported biological criteria to identify Mg deficiency in the DONMAG cohort indicates an increased prevalence of Mg deficiency in patients with decreased bone mineral density (BMD) [n = 41, M/F 2/41]. Plasma ionised Mg and total erythrocyte Mg levels prove lower in osteopenics-osteoporotics as compared to controls, in particular in younger (50-59 y) patients (cases: 2.19 ± 0.16 mmol/l; controls: 2.43 ± 0.21 mmol/l). Whereas the negative correlation between total erythrocyte Mg levels and BMD appears linked to an age effect, the positive correlation (r = 0.46) found in the younger (50-59 y) cases between plasma ionised Mg and the Z-score, as obtained from the BMD of the femoral neck of the younger cases appears more meaningful. The BMD obtained at the femoral neck also negatively correlates to the fractional urine Ca excretion [r = 0.47]. According to the abovementioned criteria, the prevalence of Mg deficiency is thus 27.5% in this study cohort, which is the largest prevalence we were able to demostrate in the various target groups of the DONMAG II cohort: 1 case present with hypomagnesaemia, 4 cases with a hypocalciuric (Gitelman-type) Mg deficiency and 4 with a hypercalciuric (Bartter-type) Mg deficiency. A task force has thereafter been created in Switzerland to addres the following issues: a) role of Mg deficiency in bone accretion during adolescence and early adulthood; b) role of Mg deficiency in postmenopausal osteoporosis in women, as well as in osteoporosis from other causes in both men and women; c) effect of oral Mg supplementation on bone accretion in Mg-deficient adolescents; d) effect of antiresorptive

agents on Mg metabolism, and e) effect of oral Mg supplementation in on bone health in Mg-deficient postmenopausal women.

Magnesium and the allergy

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It was noticed from some time the propensity of patients with hypomagnesiemia for developing allergic manifestations. This is due to the diminishing of IgA, IgG and IgM production, with consecutive IgE increasing. Another possible mechanism is in relation with increased receptors activity.
Aim of the study: Authors aimed to study the benefit of magnesium administration in allergic state. This benefit was not evaluated in the moment of allergic manifestations, but in specially after correcting the magnesium deficit.
Materials and methods: We studied 112 children hospitalized in Pediatric Clinic II during a two years period, with several allergic manifestations: allergic rinites, cutaneous allergic manifestations, and digestive allergies. All patients had ages between 1 and 18 years, both sexes being studied. After administration in hospital and clinical evaluation, all patients had biological exams including determination of magnesium serum level. In 72 patients a hypomagnesiemia was noticed. After the treatment of allergy through usual methods, the magnesium deficiency was correted by oral administration of Magnerot or Mg + B_6 Vitamine.
Results: During one year we followed this patients for allergic manifestations. We noticed a diminishing of allergic manifestations and the frequency of their appearance in more then 50% of the patients with hypomagnesiemia. We mention that many patients with allergic manifestations had not certify the athopic status, those being primary manifestations.
Conclusions: Therapy with magnesium for correcting the magnesium deficit in allergic status can be benefic through the diminishing of allergic manifestations intensity and frequency. Therapy with magnesium corrected the other symptoms of hypomagnesiemia, in particular the neuromuscular ones.

Hepatoprotective effect of MG-ginsenosides on the antioxidant system against free radical attack

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In the present study we examined the hepatic injury evoked by CCl_4 in rats and explored Mg-ginsenosidees as protective agents. 32 male wistar rats were randomly assigned in 3 groups and one of them (I) was supplemented with magnesium (Cl_2 Mg, 1000 mg/L) from drinking water. All rats underwent i.p. administration of 1.6 ml/Kg of one of the following: a solution of 0.25 g/L of ginsenosides Rb_1, Rb_2, Rg_1 and Rc, groups I (n = 8) and II (n = 8); physiological saline, group III (n = 8). Six hours later rats were treated i.p. with a 20% solution of CCl_4 in olive oil at 3 ml/Kg. 18 h later rats were killed and liver were analyzed for Total Antioxidants Status (TAS) by a colorimetric Kit; lipid peeroxidation in terms of Tiobarbituric Acid Reactive substances (TBARs) and histological examinations. We found that the different treatments have a significant effect on TAS, TBARs and lipid metamorphosis. The TAS were considerably higher in the group that received only physiological saline (III) than in groups I and II. These have a similar increase in TAS as a reactions to the acceleration of pro-oxidant process by CCl_4. However, group II revelaled more potent protection against CCl_4-induced lipid peroxidation than group I. On the other hand, the highest degree of hepatocyte damage was observed in group III and the most significant reduction in liver damage rate was found in group I which received ginsenosides and magnesium supplement. Taken together, our present results indicate that the mechanism of hepatoprotection by magnesium may be distinct from that of ginsenosides studied.

The role of magnesium in treatment of status asthmaticus and asthma attack

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Starting from several studies published in medical literature wich reveal the role of magnesium in the treatment of status asthmaticus at patients with no answer to current therapy, authours used magnesium in status asthmaticus and asthma attack at patients hospitalized in Pediatric Clinic II.
In asthma, magnesium act by facilitating calcium entering in endoplasmic reticulum and, as a result, blocking calmoduline activation and consecutively blocking miosin-kynase activation and the contraction. Magnesium interferes in asthma also by stimulation of adenylate-cyclase with increase of cAMP and facilitation of broncho-dilatation.
Aim of study: Authors aimed to estimate the benefit of magnesium in status asthmaticus and asthma attack, associating magnesium therapy with specific asthma medication.
Materials and methods: We studied 6 patients with status asthmaticus and 82 patients with asthma attack. Patients received 50 mg/kg dose of magnesium i.v. alongside specific asthma therapy. This study was performed during 4 years (between 1996 and 2000). Alongside we studied another group of patients with asthma attack who were treated with specific asthma therapy only.
Results: Using magnesium therapy, we obtained shorter attack duration, a faster improvement of symptomatology and a shorter period of hospitalization. In status asthmaticus with no response at usual therapy, all 6 patients had a good answer at usual therapy after receiving magnesium therapy.
Conclusions: The use of magnesium in adequate doses in status asthmaticus and asthma attack has a benefic action.

Magnesium and cancer in clinical practice

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The regulation of the cell cycle control and the apoptosis, of the DNA repair, depends on many enzymatic reactions which are modulated by magnesium. As a consequence, the relations between magnesium and cancer were the topic of numerosus estudies. *In vitro*, its role on cell proliferation is negligible and depends on the model investigated and on the experimental conditions. However, the Mg has a protective effect on some DNA lesions, and can have carcinogenic inhibition in some models. Otherwise, from animal studies, low magnesium diets do not inhibit growth of tumor xenograft.

Hypomagnesemia may become symptomatic in cancers. Cytotoxic chemotherapy frequently induces hypomagnesemia and renal magnesium loss through its renal tubular toxicity. The clinical studies show that it can be dangerous if no corrective measures of this hypomagnesemia are initiated. Mg supplementation could compensate or prevent the effects of anticancer chemotherapy.

In conclusion, the relationship between magnesium and neoplastic disease is rather complex and not directly applicable in clinic. On the other hand, it is demonstrated that the correction of hypomagnesemia is a therapeutic measure susceptible to improve the treatment safety and the patients comfort.

Intracellular magnesium content in hair and ionised magnesium content in blood serum in patients with arterial hypertension and influence of Slow Mag B6 supplementation on the chosen laboratory and clinical parameters

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The aim of the study was to estimate intracellular magnesium content by biochemical analysis of hair, and ionised magnesium concentration in blood serum in 92 patients with primary arterial hypertension, previously not treated or treated with the following agents ACE inhibitors, beta-blockers, calcium channel blockers and diuretics. Moreover, the patients answered the questionnaire in order to evaluate the clinical symptoms or magnesium deficiency. These patients were from General Practice Unit of Pomerania Medical Academy in Szczecin and they were treated by monotherapy of hypertension minimum from 6 months. The control groups was 18 patients with not pharmacology treated primary hypertension and also 100 blood donors in good health.

In case of laboratory deficiency of magnesium and positive answer on three questions of magnesium shortage symptoms questionnaire, these patients were qualified to 6 weels magnesium supplementation by Slow Mag B6 preparation in dose 320 mg per day.

After 6 weeks of magnesium supplementation the concentration of ionised magnesium was studied once more, and control blood pressures were re-taken. The studies revealed significant increase of ionised magnesium concentration: in ACE group patients from 0.48 to 0.59 mmol/l, in beta blockers from 0.46 to 0.55 mmol/l, in Ca channel inhibitors from 0.47 to 0.57 mmol/l and in diuretics treated patients from 0.49 to 0.57 mmol/l. We have noticed decrease in both systolic and diastolic blood pressure values after magnesium supplementation, in case of systolic blood pressure on an average about 13-16 mmHg and in case of diastolic blood pressure about 5-9 mmHg.

We noticed decrease of frequency most of investigated clinical magnesium deficiency symptoms after 6 weeks of magnesium supplementation as addition to previous hypertension therapy.

Serum magnesium concentration in patients with essential arterial hypertension associated with hypophosphatemia

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The high frequency (62.5%) of hypophosphatemia in patients with essential arterial hypertension (EAH) prompted the consideration of this element as a marker of the disease. This paper summarizes the results of investigating the serum Mg concentrations in hypertensive patients with hypophosphatemia. The study included 83 patients with EAH in which serum inorganic phosphorus (P_i) was over 0.80 mmol/l (19 in stage I, 46 in stage II, and 18 in stage III of the disease), 51 patients with EAH in which serum P_i concentration was less than 0.80 mmol/l (7 in stage I, 33 in stage II, and 11 in stage III of the disease), and a control group of 25 individuals with normal arterial tension (AT).

Patients treated with Mg salts of other drugs that might have influenced serum Mg and P_i levels were excluded from the study. Serum Mg and P_i concentration were assessed in fasting conditions using the Zeiss flame photometer.

In patients with EAH associated with low P_i level the frequency of hypomagnesiemia was higher in stages I and II of the disease (28.6% and 30.30% respectively) as compared with patients with normal P_i levels (5% and 13% respectively). In stage III of the disease the situation was reversed, hypomagnesiemia was more frequent in patients with EAH associated with normal serum P levels (17.8% vs 0). At the same time, the frequency of hypomagnesiemia in the control group was 4%. The mean values of serum Mg are significantly lower ($p < 0.05$) in all patients with EAH associated with hypophosphatemia, regardless of the stage of the disease. The value of the Mg/P_i ratio was smaller in hypertensive patients with hypophosphatemia for stages I and II of the disease, while in stage III of the disease the value of the Mg/P_i ratio was higher in hypertensive patients with P_i ratio was higher in hypertensive patients with P_i levels < 0.80 mmol/l.

In patients with EAH the high frequency of hypomagnesiemia along with hypophosphatemia as compared with patients having normal mean values of serum P_i and low mean values of Mg points to the role of both hypomagnesiemia and hypophosphatemia in the mechanisms of blood pressure increase, the increase of cellular energetic potencial as determined by the shift of serum P_i to the tissues.

KEY WORDS: *Magnesium, calcium, phosphorous, essential arterial hypertension, hypomagnesiemia.*

Oral magnesium supplementation improves exercise tolerance, exeercise-induced angina and quality of life in patients with coronary artery disease

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The impact of magnesium (Mg) supplementation on exercise tolerans, exercise-induced angina, and quality of life (QOL) in stable coronary artery diseasse (CAD) patients has not been assessed, despite the fact that Mg depletion is common in CAD patients.
Methods: In a multi-center, randomized, prospective and double-blind trial, 187 stable CAD patients [151 men, 36 women, mean age (± SD) of 63 ± 10 years, range: 42-83], were randomized to receive either Mg oxide orally (Magnosolv® -Granulat, 30 mmol/day, Asta Medica, Vienna, Austria) (n = 94) or placebo (n = 93) for 6 months. Sympton-limited exercise testing (Bruce protocol) was performed and QOL questionnarires were completed both at entry and at 6 months post intervention. Intracellular Mg levels ([Mg]i) were assessed in 114 consecutive patients from sublingual cells by X-ray dispersion [normal values (mean ± SD): 33.9 ± 4.0 mEq/l].
Results:

Exercise duration at	Magnesium (n = 94)	Placebo (n = 93)	p-value
Entry (min ± SD)	8.1 ± 2.6	7.8 ± 2.9	0.1670
6 months (min ± SD)	8.7 ± 2.1	7.8 ± 2.8	0.0075
p-value	0.0104	0.1624	

Mg therapy significantly increased post-intervention [Mg]i compared to placebo (3.5 ± 3.7 vs 32.6 ± 2.9 mEq/l, $p < 0.02$; respectively). At 6 months exercise-induced angina was significantly higher in patients who received placebo compared to Mg (19 vs 6%, $p = 0.0237$; respectively). QOL also significantly improved in the Mg group even after one month and continued to improve, compared to no significant improvement in the placebo group ($p < 0.01$).
Conclusion: Mg intervention significantly improves exercise tolerance, exercise-induced angina, and QOL in estable CAD patients.

The role of magnesium in the genesis of the distrurbances of the rhytm of the heart

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The relationship between the deficiency in magnesium and the cardiac disease was not enough studied in the pediatric pathology. The rhythm disturbances are the result of three electrophysiological mechanisms: automatism disorders, conductibility disorders and combined patterns of these two mechanisms. The magnesium interferes with the myocardial function (decreases the myocardial excitability and conductibility) and contributes to the maintaining of the potassium inside the cells. The deficit in K as a consequence of the deficit in Mg is not treatable by the administration of the K. A low Mg/Ca ratio may contribute to the apparition of the spasms of arteries.
Our study contains 160 children with the age between 3-16 years diagnosed with hypomagnesaemic tetany and who had also: a)«the click-murmur syndrome» (mitral valve prolapse)-in 23 patients (14.4%); b) borderline hypertension-in 19 patients (11,9%), and c) migraine-in 54 patients (36.2%).
These children had EKG and echocardiografic anomalies confirming the presence of a hiperkinetic cardiovascular syndrome. Regarding the disrhytmies, we found the presence of the paroxysmal supraventricular tachycardia (in 5 cases), of the ventricular extraystoles (in 5 cases) and of the LG syndrome (in 2 cases). The drug induced pathology, the myorcardial lesions and the metabolic disturbances (hypoxia, acidosis, hypoglucemia, hypo and hyperpotassemia must be excluded. The magnesium therapy leaded to the reduction of the functional signs and to the amelioration of the EKG disturbances, justifying the use to the magnesium in the current practice.

Longitudinal study of the electrocardiografic alterations in hypomagnesemic rats

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Introduction: Hypomagnesaemia causes neuromuscular, psychiatric, respiratory and circulatory condition. Such symptoms appear when Mg levels are under 1 mEq/l. Cardiac alterations vary from enlargement of QT interval, to ventricular fibrillation and heart failure. However, the sequence of the appearance of clinical evidence is unknown.
The aim of this study is to produce a reliable model in order to clarify the order in which theses symptoms may appear in Mg deficiency.
Material and methods: Twenty-five Sprague-Daley female rats, 50 g weight were divided in two groups: the first one composed by 15 rat received a Mg deficient diet (106.94 mg of Mg/kg weight), the second group (10 rats) was fed on a similar diet plus a Mg supplementation to achieve a final concentration of 493 mg of Mg/kg weight. All rats drank deionised water for a 2-month period. All rats had daily ECGs taken starting from the 5th day of the study and during a two-month period. At the end of which, the animals were anaesthetised with Nembutal and a blood sample was taken Mg in serum was determined by atomic absorption spectrophotometry. The ECG study was done in derivation II, and at least one minute of stable register was pursued. None of the animals were anaesthetised. A Multilaboratory electro cardiographer Multi Lab Of Ad Instruments was used. Results were checked with The Chart program. The statistical analysis was carried with the Stat View program.
Results and conclusion: The alterations found included: Auricular Flutter, enlargement of PQ space (individually), Q waves, enlargement of ST, U waves and the appearance of extrasystolia.The most significative were the negativization of QRS complex. These alterations appeared systematically after 15 days of deprivation, being

difficult to register in the first two weeks of study. The sequence of events was not similar in all rats. At the end of the experiment, Magnesium serum levels oscillated about 0.76 ± 0.16 mEq/l.
In conclusion, in these conditions electrocardiographical alterations were found after 15 days, being the negativization of QRS complex the most significative change. Further analysis will be needed to clarify the sequence of events.

Effects of sweat loss induced by treadmill exercise on magnesium and calcium homeostasis in franches-montagnes horses

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The physological consequences of magnesium and calcium loss via sweat during a prolonged exercise test was investigated in ten stallions. The test on a high-speed treadmill consisted of 6 trot-intervals of 20 min each at 3.0 m/s. Blood samples were collected 1 hour before the exercise test, after each trot-interval and after 1 and 2 hours of recovery. The body weight loss ranged between 19 and 25 kg with a mean reduction of the body mass of 3.71% ± 0.45 which implied a production of 14 to 16 L of sweat. Mean total magnesium concentration decreased continuously during the exercise and the first hour of the recovery period. Mean erythrocyte magnesium concentration decreased during the last two trot intervals and was significantly lower during the second hour of recovery. The mean total calcium concentration decreased during the exercise test and increased during the recovery period. Mean PTH serum concentrations at the end of the test were significantly higher. Serum $1,25(OH)_2D$ concentrations did not change with time. Assuming a concentration in the sweat of 1-6 mmol/L for Mg and 2-6 mmol/L for Ca, an approximate amount of 0.3-2 g of Mg and 1-4 g of Ca may have been excreted. According to the results of the present study, additional Mg and Ca supply are superfluous in the case of a single prolonged exercise. However, high dietary supply may be beneficial in hard working and heavily sweating horses to prevent the occurence of critically low ionised magnesium and calcium values.

Urine fractional calcium excretion as a biomarker for uncovering magnesium deficiency in humans

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Uncovering Mg deficiency in normomagnesaemic individuals remains difficult in routine. The DONMAG II substudy indicated that Mg deficient cases presented with an unexpectedly high urine fractional Mg excretion. Similar data were brought at the same time from experimental studies in MGL mice. Taking advantage from the increasing knowledge on Mg transport systems and both inherited and acquired disorders of renal Mg handling, we started a prospective study on a series of 100 consecutive patients from the DONMAG cohort that were studied from January 1st, 2001. The aim of this study was to assess the role abnormal renal Ca handling might play in the predisposition to Mg deficiency. Ca, Mg and creatinine levels were thus measured in the second morning urine obtained after an overnight fast. The results suggest that disorders of Mg metabolism are best uncovered in normomagnesaemic individuals by using an algorhythm based on the urine Ca-to-creatinine ratio (CCR). Hypocalciuric cases (CCR < 0.16 mmol/mmol) are associated with either hypomagnesuria and a trend towards hypermagnesaemia (referred to as «hypocalciuric hypercalcaemia-type»), or a relative hypermagnesuria and a trend towards hypomagnesaemia (referred to as «Gitelman-type»). Hypercalciuric cases (CCR > 0.55 mmol/mmol) are associated with hypermagnesuria and a trend towards hypomagnesaemia (refered to as «Bartter-type»). Normal Mg balance is achieved in normocalciuric cases, whereas latent or overt Mg deficiency can be demostrated in both «Gitelman-type» cases using the urine Ca-to-Mg ratio, as further confirmed by reduced plasma ionised Mg and total erythrocyte Mg levels, as well as by changes obtained after on oral Mg supplementation course (360 mg/d for 3 months). Applying this algorhythm for a retrospective assessment of the DONMAG II cohort (n = 336) also proved appropriate for identifying Mg deficiency cases. This algorhythm may prove quite helpful to shed more light on the role of Mg deficiency in health relevant hazards and offer a useful means to stratify patients in case of clinical trials.

Increasing amniotic fluid magnesium concentrations with stable maternal serum levels

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Objective: To determine the effect of prolonged maternal intravenous magnesium sulfate ($MgSO_4$) administration on amniotic fluid and serum concentrations of magnesium in preterm labor patients.
Study design: Patients at 24-34 weeks of singleton gestation, who presented with contractions (≥ 8 in 60 minutes) had amniocentesis to rule out intrauterine infection, after signing an informed consent. As part of the clinical management of preterm labor some of these women received intravenous $MgSO_4$, 4g loading dose followed by 2 g/hour maintenance dose. For technical reasons some patients had amniocentesis performed before initiation of $MgSO_4$ (controls) while others had the procedure during tocolytic therapy (study patients). Duration of treatment until amniocentesis was recorded and blood samples were drawn at that time. Maternal serum and amniotic fluid magnesium levels were measured using a colorimetric endpoint method. Data were evaluated using Student t test and linear regression analysis.
Results: Magnesium levels in maternal serum and amniotic fluid in the treatment and control groups are presented in the table. Duration of $MgSO_4$ treatment ranged from 3 to 22 hours. The positi-

ve correlation between amniotic fluid magnesium concentrations and therapy time was highly significant (correlation coefficient = 0.89; P < .001), while maternal serum levels remained stable (correlation coefficient between maternal serum levels and time = –0.39; P = .34).

Values in mg/dl	NaCl-controls (n = 31)	Mg-study (n = 10)	P within groups
Maternal serum	1.74 ± 0.21	4.01 ± 0.41	< 0.0001
Amniotic fluid	1.41 ± 0.18	2.28 ± 0.53	< 0.001
P between groups	< 0.0001	< 0.0001	

Conclusión: Although maternal serum magnesium levels remained stable with intravenous $MgSO_4$ tocolytic therapy, concentrations continue to rise in amniotic fluid along time. However, amniotic fluid magnesium levels never exceeded maternal concentrations throughout this study period.

The effect of magnesium sulfate ($MgSO_4$) on maternal serum (MS) and amniotic fluid (AF) cytokines concentrations in patients with preterm labor

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Objective: Cytokines are associated with the mechanism of preterm labor and may also be involved in fetal brain damage. We evaluated the effect of maternal $MgSO_4$ administration to patients with preterm labor on MS and AF cytokines concentrations.
Study design: Patients at 24-34 weeks of singleton gestation, who presented with contractions (≥ 8 in 60 minutes) had amniocentesis to rule out intrauterine infection, after signing an informed consent. As part of the clinical management of preterm labor some of these women received intravenous $MgSO_4$, 4 g loading dose followed by 2 g/hour maintenance dose. For technical reasons some patients had amniocentesis performed before initiation of $MgSO_4$ (controls) while others had the procedure during tocolytic therapy (mean duration 7.66 ± 6.3 hopurs; study patients). MS and AF magnesium levels were measured using a colorimetric endpoint method. Cytokines were measured using a commercial ELISA kits specific for each factor. The investigators were masked to the sample origin. Study and control groups were statistically compared using Student t test.

	Controls	Controls	Mg-study	Mg-study	P Value
pg/ml	MS (n = 26)	AF (n = 26)	MS (n = 10)	AF (n = 10)	MS/AF
TNFα	2.3 ± 3.8	0.3 ± 1.1	3.6 ± 5.33	0 ± 0	0.44/0.33
IL-1β	4.3 ± 10.8	14.7 ± 44.2	0 ± 0	17.9 ± 50.5	0.24/0.87
IL-6	0 ± 0	149.6 ± 211.8	0 ± 0	171.1 ± 178.3	1.0/0.81
IL-10	54.8 ± 93.8	11.2 ± 21.5	80.0 ± 82,4	14.3 ± 19.9	0.50/0.72

Results: Mean magnesium levels in MS rose by 230% and in AF by 162% in the treatment group as compared to controls (P < 0.001). Cytokines levels in MS and AF are presented in the table.
Conclusion: Maternal $MgSO_4$ administration to patients with preterm labor had no effect on MS and AF cytokines concentrations. These results suggest that the mechanism of magnesium as a tocolytic agent may not be mediated via the examined cytokines.

Yield, sugar composition and ratio of mono- and disaccharides in carrot varieties as affected by mg leaf fertilisation

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As the Mg content of food vegetables is of paramount importance growers have to be acquainted with the Mg supply and availability of the soil during cultivation. In case of insufficient Mg content of the soil steps must be taken to supply it, e.g. with leaf fertilisation. It has the advantage that nutrient elements are easily even on dry, unirrigated areas.
In our field trials on meadow silt soil, the effect of Mg leaf fertilisation was studied on 5 Hungarian carrot varieties (Szupra, K-arany, Flakker, Rekord, Fertödi vörös) under irrigated and rain-fed conditions.
Multifactorial trials included first: uniform water supply during the growing period (150 mm misro-sprinkler irrigation) and natural precipitation, respectively and second: 1% MgS04 leaf fertilisation (2 (dl/M2) applied twice during the growing period. Measurements involved marketable yield (kg/m2), sugar content (%) and composition (glucose. Fructose, sucrose) as well as the ratio of mono- and disaccharides.
Results indicated that in the irrigated treatments Mg leaf fertilisation only increased yield by 6.08% in the average of varieties while under rain-fed conditions the ratio was 43.94%.
In the year 2000 the quantity of natural precipitation during the growing period was very low (213.7 mm), thus. The impact of Mg leaf fertilisation was masked by the stronger effect of the uniform water supply.
The yield of irrigation plots was 4.15 kg/m^2 in the average of varieties and Mg treatments while 2.65 kg/m^2 in unirrigated plots. This also seems to be proved by the higher treatment effect of Mg fertilisation in rain-fed plots.
In dry periods yield could be increased by Mg leaf fertilisation due probably to the prolongation of foliage life (photosynthesis capacity) of carrots.
In irrigated plots Mg leaf fertilisation increased the quantity of-monosaccharides (glucose, fructose) at the expense of sucrose concentration. In sum, the lowe monodisaccharide ratio, which affects root maturity favourably, was increased by 150% by the Mg treatment.
In rain-fed areas Mg leaf fertilisation increased sucrose concentration (by 26.36% in the average of varieties) resulting in increasing total sugar quantity and improving (lowering) the ratio of mono- and disaccharides in almost every variety.

Thus, Mg leaf fertilisation results in more favourable sugar composition and higher sugar content, that is, higher storability under rain-fed conditions.
The favourable effect of Mg treatments on quality could not assert at higher soil moisture content as the vegetative growth of plant opposed to the maturity of roots.

Relative apparent and true intestinal magnesium absorption are not influenced by the dietary magnesium levels in rats; a total magnesium and stable isotope magnesium study

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The magnesium is mainly absorbed in the low parts of the intestine and its absorption is not or very little controlled. Many *in vitro* and *ex vivo* works showed that the absorption of Mg occurs primarily by passive way. The aim of this study is to determine whether the Mg intake can or not influence apparent and true intestinal absorption of Mg in rats. In that aim, thirty male Wistar rats were for 7 days the basal semi-purified diet, containing 600 ppm of Mg. Groups of 110 rats were then fed for 28 days the basal semipurified diet with different levels of Mg 150, 300 and 600 ppm of Mg apparent and true intestinal Mg absorption as well as Mg status indices were determined at the beginning and at the end of the experiment. Our findings show that the percentage of intestinal Mg absorption was statistically similar among the three experimental groups at both stages of the experiment. In line with this are the results obtained with the stable isotope technique which show that the percentage of intestinal ^{25}Mg absorption was also statistically similar among the three experimental groups. Consequently, both the absorbed amount and the endogenous excretion of Mg were proportional to the intakes of Mg. These results confirm that passive para-cellular transport of Mg is the predominant component of intestinal Mg absorption in rats at usual dietary Mg intakes. Moreover, our data confirm also that intestinal Mg absorption is not conditioned by the body status or requirement of Mg or subject to any adaptative mechanism.

Dynamics of magnesemia in school stress

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Working hypothesis: The role of magnesium in the stress reactions is known, Mg being called the stress electrolyte (Durlach, 1988). The authors undertook the study of magnesemia in high school students exposed to a condition of psychic suprasolicitation, and of the relationship between serum magnesium with the possible clinical symptoms.
Materials: The investigation were carried out in 100 healthy students of the 11th grade of the high school aged between 17 and 18 years. The sex distribution was: 29 girls and 71 boys. The stress chosen was the written test in mathematics. Magnesemia was determined before and after the intellectual effort and an inquiry was simultaneously made concerning the condition of the students. Magnesemia was determined by photometry.
Results: The magnesemia levels before and after the mathematics written test at the first class of the school activity were within physiologic range in all subjects. No subjective clinical manifestations were detected. After the mathematics written test a statistically significant reduction ($p < 0.005$) of serum Mg was noted to mean levels of 2.04 ± 0.47 Mg/100 ml before the stress, reaching mean values of 1.83 ± 0.40 Mg/100 ml after stress. No statistically significant differences were noted in the concentration of magnesemia before and after stress between the girls and boys.
Conclusion: The mathematics written test in high school students constituted a stress. One of the biochemical manifestations of the stress reaction was hypomagnesaemia probably produce by the disturbance of the relationship between intra- and extra-cellular Mg by the kelation of Mg ions by the fatty acids in excess released in the conditions of stress and by the increased hormonal loss.

Changes in Mg^{2+} and other cations' plasmatic concentration in patients with depression

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We determined plasmatic concentrations of Mg^{2+}, Cu^{2+}, Fe^{2+} and Mn^{2+} at patients with severe depression admitted in psychiatric clinic. We studied 76 adult patients, with age ranged between 18-70 years. Depression intensity was assessed with Hamilton scale. Determinations were performed in the moment of admittance and 30 days after beginning of the treatment. We include in the study patients with medium or severe depression (score over 16 on Hamilton scale) and exclude patients with cirrhosis, chronic renal failure, heart failure, alcoholics). In hospital, all patients had same diet and life condition patients were treated with tricyclic and tetracyclic antidepressant and also with selective serotonin reuptake inhibitors (SSRI). Hospitalization of all patients overpasses 30 days. It was determined Mg^{2+} adn other bivalent cations plasmatic level. Data obtained were statistically interpreted. We compared initial values vs. data after 30 days of treatment, but also initial values vs. data in normal subjects with similar age and gender characteristics. Data obtained show a moderately decrease in Mg^{2+} plasmatic level in patients with depression vs. normal subjects (22.9 ± 3 mg/dl in normal group vs./20.2 ± 2.1 mg/l in patients with depression, NS). Taking in consideration only patients with severe depression (score over 23 in Hamilton scale) difference were significant 17.8±2.1 in group with severe depression vs. 22.9 ± 3 mg/l in normal group, $p < 0.05$). Cu^{2+} increases significantly in group with severe depression (0.8 ± 0.15 mg/l in group with depression vs. 0.63 ± 0.12 mg/l in normal group, $p = 0.016$) and plasmatic levels are not changing significantly. We could not establish correlation between antidepressant therapy and evolution of plasmatic level of cations. We consider that a lower Mg^{2+} level and an increase in Cu^{2+} level might be involved in evolution and severity of depression.

Influence of nocturnal activity on magnesemia in an industrial colectivity

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Working hypothesis: Changes in magnesium metabolism were detected during exercises in relation with the type and duration of the exercise. The physical and psychomotor effort increased Mg requirements.
Aim of the investigation: Assessment of magnesium in the workers in food industry carving oot their activity in night shifts has a stronger impact on the organism as compared with the diurnal activity.
Materials and methods: The investigations were carried out in 72 healthy employees of a bread factory with mean age of 40 years. The sex distribution was: 55 females and 17 males. Magnesemia was determined by photometry immediately after the night shift and was compared with the levels found at the end of the day shift.
Results: The levels of magnesemia found after the nocturnal activity showed the tendency to decrease, without revealing statistically significant differences between the levels of serum magnesium during the diurnal activity and the nocturnal activity respectively. Because the industrial population was predominantly femenine, the possible sex-related differences in magnesium were investigated. Higher magnesium consumption was found in women after the night shift, but the sex-related differences were not statistically significant. In the age groups the lowest levels of magnesemia were found in the age group 41-50 years.
Conclusion: The nocturnal activity carried out in an industrial collectivity does not represent a major physical and psychomotor solicitation as compared with the diurnal activity. No statistically significant differences were noted in magnesemia during the nocturnal and diurnal activity, respectively.

Clinical manifestations of hypomagnesiemia in chronic hepatitis in children

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Background: Magnesium is the second most important intracellular electrolyte after potassium and by his enzymatic catalyst function is involved in all cellular metabolic phases. The common signs of magnesium deficiency are of great variety and are nonspecific, without relationship between their intensity and the degree of deficiency.
The aim of the study was to analyze the frequency of clinical manifestations in post-viral chronic hepatitis related with hypomagnesiemia to find a better attitude for therapy.
Material and method: We have studied 138 children, age between 8 months and 18 years, hospitalized in our clinic during a period of 8 years for chronic hepatitis B under classic liver protection therapy. In all patients a very detailed anamnesis and clinical examination were done. Beside the biochemical tests specific for liver diseases, serum electrolytes determination was done at 1 month, maximum 3 months interval. Magnesium determination was done using colorimetric method with xilidil blau.
Results and discussions: Clinical symptomatology that could be related with deficiency of magnesium (excluding other causes by clinical and paraclinical criteria) was: muscular cramps, members paresthesia in 34 patients (24.64%), precordial pain in 14 patients (10.14%), abdominal pain, abdominal distension in 50 patients (36.23%), headache in 47 patients (34.06%), lipothmia in one patients (0,72%), anxiety, asthenia, restlessness sleep in 75 patients (54.35%). Hypomagnesiemia was detected in 99 patients (71.74%). All patients with low serum magnesium (1.6-1.3 mEq/l) had some mentioned symptoms, but not al patients who presented the symptomatology had also hipomagensiemia. Symptomatology disappeared in 86.2% of patients after magnesium products with increase of magnesium level even that only few cases had normal valvues of magnesium.
Conclusions: Even that the mechanisms of hipomagnesiemia in chronic hepatic diseases are not fully known, hipomagnesiemia is frequent in chronic hepatitis B. Normal values of serum magnesium does not exclude a magensium deficiency. Treatment with magnesium products is a precious adjuvant in treatment of chronic hepatitis B.

Magnesium deficiency in alcolics and how it may come

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Most tables summarising causes of mangesium (Mg) deficiency shows alcoholism, although there are only few original data available. Therefore we put the question if there is Mg deficiency in alcoholics and whether aldosterone (ALDO), parathyroid hormone (PTH) or nutritional factors play a pathogenetic role.
41 patients were examined during a standardised alcohol withdrawal treatment. The first day we measured Mg and creatinine in serum and 24h-urine as well as Mg in erythrocytes by means of clinical routine methods. ALDO and PTH were measured by means of RIA. Three groups were built by randomisation. Group I received no medication, group II was given 5 mg Mg/kg body weight daily and group III received 150 mg spironolactone per day. After three weeks the data of the Mg status were taken again. Values are given as means ± SD.
Initial Mg in serum was 0.79 ± 0.12 mmol/l. After three weeks data did not differ from the beginning and there were no differences between the groups. Mg in erythrocytes was low (1.50 ± 0.17 mmol/l) compared with normal values (1.6-2.0 mmol/l). Initial Mg excretion in 24 h-urine samples was 2.14 ± 1.39 mmol/d which is below the reference inteval of 2.4-8.3 mmol/d. At the end of the study Mg excretion increased to 3.93 ± 2.31 mmol/d without differences between the groups. No statistical correlation was found between Mg excretion in 24 h-urine and ALDO or PTH.
The present data shows normal Mg serum levels. But we found lowered values for Mg in erythrocytes and basal Mg excretion as indicators of Mg deficiency. Iin this study, neither PTH nor ALDO could be identified as causal factors of Mg deficiency in alcoholics. Since there is an equal increase of the urinary Mg-excretion in all groups, we conclude that nutrition might play an important role in the generation of Mg deficiency in chronic alcoholic patients.

Mechanisms of Mg^{2+} transport in nerve cells

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Direct measurements of intracellular free Mg^{2+} concentration ($[Mg^{2+}]_i$) in neurons were first reported in the early 80's by Álvarez-Leefmans and coworkers, using ion-selective microelectrodes[1,2]. These measurements were done in identified neuronal cell bodies of the suboesophageal ganglia of the snail, *Helix aspersa*, a traditional model to study ion transport in nerve cells. The mean basal $[Mg^{2+}]_i$ was 0.66 ± 0.05 mM and the simultaneously recorded transmembrane voltage E_m, was -52.4 ± 3 mV. It was concluded that $[Mg^{2+}]_i$ was lower than predicted for a passive distribution implying the presence of an outwardly directed active extrusion mechanism. These measurements were later confirmed[3] using double-barreled microelectrodes containing the neutral ligand ETH 5214, that has better selectivity for interfering ions than the sensor we used previously (i.e. ETH 1117). The nature of the mechanisms for Mg^{2+} extrusion in neurons is largely unknown and is the focus of our current research. Like in many preparations investigated so far, including invertebrate glial cells[4], we have found that one of the extrusion mechanisms is dependent on the presence of external Na^+, consistent with a Na^+/Mg^{2+} exchanger. The stoichiometry of this mechanisms must be electroneutral since we have demonstrated that Mg^{2+} movements occur through the plasma membrane unaccompanied by changes in E_m and changes in the latter in the range between –70 and– 20 mV during transmembrane current pulses lasting up to ~ 10 min affect neither basal $[Mg^{2+}]_i$ nor the rate of Mg^{2+} influx. This is in contrast to what has been reported in leech neurons[4]. Na-dependent Mg^{2+} efflux is blocked by amiloride (1mM). In barnacle muscle fibers it has been postulated that Mg^{2+} extrusion is coupled to Na^+, K^+, Cl^- entry. The latter has been proposed to occur through a protein sharing various properties with the bumetanide sensitive Na^+, K^+, $2Cl^-$ contransport[4], although Mg^{2+} extrusion is less sensitive to bumetanide than the triple cotransporter. However, in *Helix* neurons, Na^+ -coupled Mg^{2+} extrusion is insensitive to bumetanide (100 µM). So far our results are only consistent with the presence in these neurons of an electroneutral Mg^{2+} extrusion mechanism coupled to the Na^+ chemical gradient.

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