A guided tour of presentations at the XIV International Magnesium Symposium "Magnesium in Health & Disease" Roma, Villa Malta, June 23-24, 2016

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doi:10.1684/mrh.2016.0405

We provide here a summary of 21 presentations by invited speakers, 12 oral communications and 25 posters.

We hope that this "guided tour" through the XIV IMS abstracts might be of help to readers, bearing in mind that all results and conclusions have been reported according to the Author's own interpretation. We apologize in advance for any errors or omissions.

Breaking News

Intracellular Mg concentration fluctuates with a circadian rhythm in both human and unicellular algal cells - suggesting a role for Mg in cellular time-keeping properties (*van Ooijen*).

Paramagnetic $^{25}Mg^{2+}$ isotope replacement of non-magnetic $^{24}Mg^{2+}$ and $^{26}Mg^{2+}$ ions with in DNApol[beta] monomer protein enzymes resulted in a sharp decrease in the catalytic activity of these enzymes (*Bukhvostov*) - an observation that might impact the DNA damage response to DNA-targeting drugs.

Mg^{2+} penetrates human skin primarily through hair follicles (*Barnard*).

Mg transport proteins

Mg homeostasis research and the long-known impact of Mg on human health and disease has been vastly enhanced by the discovery of specific Mg transporters (*Touyz, Bindels*), and presentations at the IMS 2016 widely disseminated this knowledge.

Human Studies

Increased Mg intake can change the gene expression of a variety of Mg transporters, while improving BP in hypertensives (*Rodriguez*) and lowering HgbA1C in overweight pregnant women (*Liu*): exercise changes Mg transporter gene expression while improving T2D risk factors (*Cheng*). In a human family with mutations in the MAGT1 gene, Mg supplementation decreased their usually uncontrolled Epstein-Barr infections (*Lenardo*).

Animal studies

Expression of TRPM6 and 7 in mice kidney and colon was inversely related to the degree of

To cite this article: Rosanoff A, Wolf FI. A guided tour of presentations at the XIV International Magnesium Symposium. *Magnes Res* 2016; 29(3): 55-9 doi:10.1684/mrh.2016.0405

hypomagnesemia, and influenced by inflammatory bowel disease (*Arduini*). Wildtype mice given a salt-aldosterone solution showed inflammatory activation of liver and spleen, similar to those found in hetereozygous TRPM7 +/1 mice (*Rios*). Wild-type or heterozygote TRPM7-kinase domain mice show anti-fibrotic effects of the TRPM7 kinase domain, suggesting that when TRPM7 is downregulated, cardiac fibrosis is promoted in aldosterone-induced hypertension (*Rios*).

See also: *Maier, Trapani, Ouadid-Ahidouch, Hardy, Cazzaniga, Luongo, Takayanagi, Wallace, Castiglioni, Shimizu*.

Conclusion

In view of the multifaceted roles of TRPM7/6 in cell biology these channels can be viewed as promising therapeutic targets. Research is focusing on this issue, e.g. TRPM7 channels can be variously modulated by pharmacological compounds (*Chubanov*).

Assessment of Mg status

Accurate and precise assessment of human Mg status remains a major challenge. Blood values (plasma or serum total and/or ionized Mg concentrations), are not reliable markers of Mg status, as they do not reflect the Mg content at tissue/organ levels. In addition, serum Mg changes only subtly with oral Mg supplementation or dietary Mg depletion, suggesting a very complex albeit efficient balance of distribution/absorption/excretion of circulating Mg. Both circulating and urine Mg measurements are used for assessing magnesium status in research, but are not fully reliable in routine clinical testing of individuals. Indeed, chronic latent Mg deficiency can occur with serum Mg values in the "normal" range. In addition, the peculiar Mg homeostasis at the cellular and tissue levels represents another bias: total cellular Mg can change acutely, while cellular Mg^{2+} ion concentrations (considered the metabolically "active form") appear to remain relatively constant (*Touyz and Others*), a situation contrasting with that widely accepted for Ca^{2+} (i.e. constant total ion, fluctuation of free).

Stable isotopes (see *Bukhvostoz)*, Mg metabolism expression (see *Rodriguez*), and new intracellular Mg dyes (see below) may help to address this great need for full, precise, and accurate Mg status evaluation (*Mazur*). For example, newly designed fluorescent indicators attached to organelle-targeting moieties can be used to detect intracellular free Mg^{2+} and Mg accumulation in mitochondria, nuclei, Golgi and whole cells (*Buccella*). Synchrotron X-ray imaging using X-ray fluorescence and X-ray transmission microscopy allows intracellular Mg concentration mapping; and when combined with atomic force microscopy permits intracellular Mg concentration mapping of single cells (*Farruggia*). Other offerings for indirect assessment include oxidative damage markers, which in competition athletes controlled for exercise and/or Mg intake, show coordination between antioxidant defenses and Mg (*Laires*). In humans, use of both total and ionized Mg in RBCs can be used to evaluate spasmophilia and the effects of Mg therapy (*Torunska*).

Human Mg requirements

Precise human balance studies in a metabolic unit suggest that 250 mg Mg intake/day should be adequate for 95% of healthy, 70 kg adults in a non-stressed environment, decreasing or increasing with body weight. Urinary Mg excretion fluctuates with Mg intake within a few days, while serum Mg remains stable for several weeks during dietary Mg depletion. These highly precise studies provide solid information that in non-stressed, healthy adults, serum Mg <0.85 mmol/L, combined with a dietary intake <250 mg/day and urinary excretion <80 mg/day, point to an Mg deficiency that would respond to oral Mg therapy (*Nielsen*). However, these assessments were made in a non-stressed environment; Mg deficiency was reported to be identified in 60% of patients with chronic stress; supplementation with Mg and vitamin B6 reduced stress symptoms, improved quality of life, and increased stress resistance (*Akarachkova*).

Mg in chronic diseases

This essential nutrient intake is considered to be sub-optimal in much of the Western world where cardio-metabolic and other chronic diseases thrive.

Low Mg concentrations promote a pro-inflammatory environment, a common denominator in many chronic diseases shown in epidemiological studies to be associated with low Mg intake and/or status (*Maier*). Cells deficient in TRPM7-kinase have shown a pro-inflammatory phenotype (*Rios*), and downregulation of TRPM7 reduces both the number and mean velocity of migrating T lymphocytes. Also, Mg influx, closely associated with aspects of inflammatory signaling, is mediated by Mag T1, one of the most selective of the Mg transporters (*Maier*).

In addition to inflammation, low dietary Mg, as well as its ratio to Ca, can impact upon certain genetic polymorphisms that enable expression of disease in humans. In addition to generally low dietary Mg intakes in the Western World, dietary calcium intakes have risen over the past 30+ years in the USA, causing an increasing Ca:Mg intake ratio >2.6 which might influence gastrointestinal neoplasia risk (via polymorphisms in three genes) as well as total mortality. Inverse associations between vitamin D status and CVD and colorectal cancer mortality are also affected by Mg intake. Epidemiological studies comparing intakes and disease states conducted in the USA with its high Ca:Mg intake ratio and China with its low Ca:Mg intake ratio suggest that Ca:Mg intake ratios between 1.7 and 2.6 may serve as an optimal ratio range for magnesium and calcium to express physiological benefits (*Dai*). Independently and comparably, a serum Mg/Ca quotient, (0.4 is optimal, 0.36-0.28 too low) has been proposed as a more practical and sensitive indicator of Mg level and/or turnover, than serum Mg in a long-term medical survey (*von Ehrlich*).

Magnesium in CVD

Mg is a second messenger that influences hundreds of enzymes and signaling molecules, including Ca^{2+} ion antagonistic actions, and as such is vastly important in the regulation of cardiac and vascular contraction/dilation (*Touyz*).

Energy-adjusted Mg intake was found to be inversely associated with CVD, cancer and all-cause mortality, and individuals with the highest Mg intakes showed a 34% reduction in mortality risk in the PREDIMED study (*Salas-Salvado*). Also, higher dietary Mg intakes reduced the risk of stroke in women (*Rexrode*). Circulating and dietary Mg, previously known to be related to soft tissue calcification in chronic kidney disease, has also been shown to be related to coronary calcification in healthy individuals (*Hruby*), and *ex vivo* analysis of Mg-incubated blood from human intervention studies show that optimal Mg has beneficial effects on platelet function (*Twomey*).

Magnesium in metabolic diseases

Dietary, tissue and serum Mg deficiencies have been associated with diabetes and metabolic syndrome. In healthy, overweight subjects, dietary Mg intake, not obesity, is associated with hypomagnesemia and hyperglycemia. In addition, a meta-analysis shows that oral Mg therapy for four months can improve fasting glucose and HOMA-IR of the metabolic syndrome (*Guerrero-Romero*).

Using data from six cross-sectional studies, an inverse association was found between dietary Mg intake and the risk of metabolic syndrome, with the highest Mg intake group having an OR of 0.69 when compared with the lowest Mg intake group (*He*). In hepatocytes, Mg deficiency increased H6PD activity and 11beta-HSD1 expression, driving the production of cortisol and decreasing insulin responsiveness (*Romani*).

In a meta-analysis of 18 RCTs, oral Mg had varying effects as regards disease progression: Mg therapy resulted in improved glucose parameters in diabetics, while providing improved insulin-sensitivity in those at high risk of diabetes (*Veronese*).

High Mg wasting can occur at an early stage of diabetes, leading to hypomagnesemia in diabetic patients. A rat study showed that TRPM6 was down-regulated in kidneys when Mg excretion was high, and downregulation of TRPM6 was coincident with down-regulation of thiazide-sensitive NCC, a principal regulator of TRPM6 expression (*Takayanagi*).

Mg and cancer

Mg's role in cancer biology and therapy is controversial as Mg deficiency can promote several steps of carcinogenesis and tumor development in animal models, but conversely, chemotherapy-associated hypomagnesemia may improve

outcome in some cases (*Trapani*). TRPM7 appears to play varying roles in several cancer cell lines, suggesting a changing role between early stage growth/migration regulation and advanced stage migration/invasion (*Ouadid-Ahidouch*). A mutation of a single amino acid in the CNNM3 Mg transporter was able to completely abolish functional complexing with PRL-2, reducing both Mg transport and tumor growth similarly to PRL-2 knockdown (*Hardy*).

Mg availability may affect cancer drug therapy response: cancer drug sensitivity to Mg was diminished in two *in vitro* cancer cell lines when acutely supplemented or adapted to a high Mg environment (*Trapani*). TRPM7 and MAGT1 as well as total intracellular Mg concentrations were found to impact drug resistance in some neoplastic cells (*Cazzaniga*), however, generalizations are premature as in other colon cancer cell lines, expression of TRPM7 differs in its effects (*Luongo*).

Mg in kidney disease

The effect of Mg administration on mortality in chronic kidney disease (CKD) has not been investigated as a priority end-point, even though Mg salts could act as a phosphate binder, lowering phosphate absorption as well as raising circulating Mg levels - a possible benefit to an ailing kidney. A meta-analysis of RCTs reported no effect of Mg supplementation on mortality in CKD, but the quality of the RCTs was poor (*Massy*). Hypermagnesuria was shown in an animal model for tubule-interstitial nephropathy to be a dysfunction of Mg reabsorption resulting from a decrease in the claudin-16 expression, a paracellular Mg transporter (*Shimizu*).

Mg and reproductive health

Mg in animal models shows several mechanistic possibilities for Mg deficiency to be connected with fetal brain, CNS and mortality issues: Mg therapy in pregnancy is routinely given to treat pre-eclampsia, to prevent seizures, and during preterm labor to protect the fetus (*Hallak*). Pregnant Russian women show high levels of Mg deficiency based on serum Mg and/or a Magnesium Deficiency Questionnaire (*Makatsariya*). Mg deficiency was also shown to be very prevalent in Russian women with other hormone-dependent conditions. Mg with vitamin B6 therapy reduced Mg deficiency and improved Mg status (*Makatsariya*).

Mg and bone health

The association of Mg with bone health, osteoporosis and sarcopenia, across all age groups and both genders, shows that Mg plays an important role in bone and muscle health during aging (*Welch*). A cell culture study showed that TRPM7 and MagT1 expression increased with early osteogenic differentiation of mesenchymal stem cells, and the silencing of either one induces expression of the other (*Castiglioni*). In a co-culture of both osteoblasts and osteoclasts, increasing Mg leads to promotion of osteoblast formation while inhibiting differentiation of osteoclasts. Similar results were obtained *in vivo*, confirming the suitability of this *in vitro* co-culture model to mimic *in vivo* conditions (*Luthringer*). These associations strongly suggest that the use of Mg implants might enable bone formation or turn-over. However, degradability of a CE-approved Mg material needs more comparative *in vitro-in vivo* research, and a reliable model for permanent implants (*Feyerabend*).

Mg and GI diseases

Low Mg plays an active role in the severity of colon inflammatory diseases. A mouse model of inflammatory bowel disease showed that reduced serum Mg could be counteracted by high dietary Mg (*Arduini*); in preliminary data, high dietary Mg attenuated, if not prevented colitis, by reducing inflammation damage of the colonic mucosa, as well as reducing loss of skeletal muscle mass (*Petito*).

Mg and skin

Mg^{2+} penetrates human skin, depending upon concentration, exposure time and number of hair follicles (*Barnard*). Deep seawater concentrate

applied to a skin model of dermal fibroblasts and keratinocytes showed Mg supplementation prevented inflammation-driven TRPM7 over-expression, while improving adhesion and migration. It is speculated that Mg supplementation has the potential to improve wound healing, regenerative capacity and biomechanical properties of skin (*Wallace*).

Mg in neuropathology and stress

Depression, anxiety & stress

A thorough, systematic literature review of Mg and depression revealed conflicting results in the large number of cross-sectional studies, and in the few prospective studies; several studies on the interaction of Mg with antidepressant medications also showed mixed results (*Martinez-Gonzalez*). A literature review of Mg in stress and anxiety studies showed that Mg could confer benefits, but the quality of the studies was generally poor, and placebo effects can be robust (*Dye*). Depressive- and anxiety-like behaviors can be found in mice after both a three- and six-week consumption of a low Mg diet (*Serefko*). This rodent model also showed that stress induces physiological translocation of Mg from brain towards serum and that Mg administration enhances the anti-depressant-like activity of NMDA antagonist, while AMPA antagonist (NBQX) reverses the anti-depressant activity of Mg (*Poleszak*). A human study measuring heart rate variability in women with chronic emotional stress (where 60% were Mg deficient according to hair analysis) showed that oral therapy with Mg and B6 decreased anxiety and increased quality of life measures, while improving LF/HF ratios which reflect sympathetic activation (*Akarachkova*).

Addiction

Chronic stress (which is linked to Mg, see *Akarachkova* and *Poleszak*) can favor addiction, and hypomagnesemia increases the vulnerability to addiction and relapse. Mg therapy decreases the intensity of addiction to opiates, cocaine, amphetamine, nicotine, cannabinoids and other addictive agents. Mg also reduces withdrawal symptoms and provides a rewarding stimulus without developing into addiction. Mg sufficiency as well as Mg therapy can reduce vulnerability to and intensity of addiction, perhaps by influencing NMDA receptors, the GABA system, the reduction of brain NOS activity, and Substance P (*Nechifor*).

Pain relief

Mg increased the "conditioned place preference" of a centrally-acting analgesic with opioid and non-opioid actions in rats, showing that Mg may enhance the pain suppression action of this drug (*Nechifor*). In a rat study, $MgSO_4$ enhanced pain relief and core body temperature-lowering effects of ketamine, a CNS anesthetic, in a synergistic way (*Vujovic*).

Blood-brain barrier

Beyond pain relief, addiction, stress, depression and anxiety, evidence of the critical role of magnesium in several neurological conditions exists. However, impairment of Mg permeation through the blood-brain barrier has slowed the clinical application of Mg for these various conditions.

Carriers such as polyethylene glycol or brain-permeable Mg salts such as Mg threonate are worthy of study (*Vink*). N-acetyltaurine Mg, a lipophilic compound that facilitates the passage of both Mg and taurine into neuronal cells, has shown promising results in treating human migraine (*Danhier*).

Mg infusion for 30 minutes improved vascular stiffness in patients with both dementia and a very high Augmentation Index (AIX, a noninvasive parameter of microvascular stiffness associated with CV mortality and Mg depletion), while oral Mg therapy seems to show similar results over some months (*von Ehrlich*).

Disclosure

Financial support: none. Conflict of interest: none.