BASICS OF MAGNESIUM HOMEOSTASIS

Lyudmila Halacheva, Nikolai Kolev, Krasimir Kostov
Department of „Physiology and Pathophysiology"
Medical University-Pleven, 1 „Kliment Ohridski” Str., 5800 Pleven, Bulgaria
E-mail: l_halacheva@abv.bg

ABSTRACT
Magnesium (Mg$^{2+}$) is the fourth most abundant cation in the human body and the second most abundant intracellular cation. It is an important structural component of bone and soft tissue cells. The strict control of blood Mg$^{2+}$ concentration is essential for many physiological processes such as cell permeability, neuronal activity, neurotransmitter release, muscle contraction, cardiac excitability, hormone receptor binding. Mg$^{2+}$ has a fundamental role as a co-factor in more than 300 enzymatic reactions involving energy metabolism and synthesis of nucleic acids. A persistent hypomagnesemia is associated with severe health risks and is involved in the pathogenesis of type 2 diabetes mellitus, osteoporosis, heart and vascular diseases. Therefore, the tight regulation of plasma Mg$^{2+}$ levels is of vital importance. Mg$^{2+}$ homeostasis depends on three organs: the intestine, which determines Mg$^{2+}$ uptake, bones that store Mg$^{2+}$ and the kidneys, which are responsible for Mg$^{2+}$ excretion.

Key words: magnesium homeostasis, magnesium channel

INTRODUCTION
Magnesium (Mg$^{2+}$) is the fourth most abundant cation in the human body and the second most abundant intracellular cation. Mg$^{2+}$ plays an essential physiological role in many functions of the body: it is important for bone mineralization, muscle contraction, neuronal activity, control of vascular tone, cardiac excitability, neurotransmitter release, hormone receptor binding and transmembrane ion flux [22]. Intracellular Mg$^{2+}$ forms a key complex with ATP and has a key role in many other important biological processes such as protein synthesis, cell replication, and energy metabolism [14]. There are multifold clinical manifestations of an altered Mg$^{2+}$ balance. Hypermagnesemia can cause neurologic and cardiac sequelae, including lethargy, confusion, coma, complete heart block, and cardiac arrest. Hypomagnesemia is associated with a wide spectrum of diseases, including type 2 diabetes, hypertension, osteoporosis and depressions [25]. Therefore, controlling and maintaining magnesium homeostasis is of vital importance.

MAGNESIUM INTAKE AND DISTRIBUTION
The normal adult human body contains approximately 22-24 g magnesium [22]. About 60% of the magnesium is present in the bones, 20% in skeletal muscles, 19% in other soft tissues, and less than 1% in the extracellular fluids. Intracellular magnesium concentrations range from 5 to 20 mmol/l: 1–5% is ionized, the remainder is bound to proteins, negatively charged molecules and adenosine triphosphate (ATP). Extracellular accounts about 1% of total body magnesium [20]. Approximately 55-70% of plasma Mg$^{2+}$ exists in the ionized, free, physiologically active form, which is important for its physiologic functions, 10-15 % is complexed with various anions such as phosphate and citrate and 20-30% is protein bound. Of the protein bound fraction, 60–70% is associated with albumin, and the rest is bound to globulins [11]. In healthy people, plasma magnesium is carefully regulated within the narrow range of 0.7-1.1 mmol/l. In order to maintain normal Mg$^{2+}$ levels, the recommended daily dietary allowance is 6 mg/kg/day. This means 400 to 420 mg/day for adult men and 310-320 mg/day for adult women [1]. The daily requirement is higher in pregnancy, lactation and following debilitating illness. Magnesium intake depends on the magnesium concentration in drinking water and food composition. High amounts of magnesium are found in nuts, green leafy vegetables such as spinach and broccoli (which are rich in magnesium-
containing chlorophyll], cereal, grain banana, and legumes. Fruits, meat, fish, and milk based products are in general relatively low in Mg [22].

**MAGNESIUM STORAGE**

Bone tissue is the largest Mg\(^{2+}\) store in the human body, where it contributes to the density and strength of the skeleton. About 60% of total Mg\(^{2+}\) is stored in the bone, one third of which resides on cortical bone on the surface of hydroxyapatite or in the hydration shell around the crystal. It serves as a reservoir of exchangeable Mg\(^{2+}\) to maintain normal plasma levels, leaching Mg\(^{2+}\) when its plasma levels drop and facilitating the synthesis of new bone when the circulating level is abundant. A recent study has found that low blood plasma Mg\(^{2+}\) concentrations lead to activation of bone resorption by osteoclasts and decreased osteoblast bone formation [21]. Bone surface Mg\(^{2+}\) concentrations are closely related to serum Mg\(^{2+}\) concentrations, indicating a continuous exchange between bone and blood [26]. The larger fraction of bone Mg\(^{2+}\) is deposited as an integral part of the apatite crystal and its release follows the resorption of bone. Fraction of Mg\(^{2+}\) stored in muscle fibres (about 20% of total body Mg\(^{2+}\)) plays an important role in the regulation of muscle contraction by antagonizing the action of Ca\(^{2+}\) [16].

**INTESTINAL ABSORPTION**

Daily dietary intake of Mg\(^{2+}\) is about 360 - 370 mg. 30-50% of ingested magnesium is normally absorbed by the intestine. Most of the absorption occurs in the jejunum, ileum, and colon. Fractional intestinal absorption of magnesium is inversely related to intake and may vary from 20 to 80%. The intestinal magnesium absorption occurs through two different transport systems acting in a parallel fashion: an active transcellular transport and a passive paracellular pathway [17].

When dietary magnesium is higher, then the majority about 90% of intestinal magnesium absorption occurs through the paracellular pathway between the enterocytes [24]. This transport depends on the transepithelial electrical voltage (which is normally about +5 mV, lumen positive with respect to blood) and the transepithelial concentration gradient. Luminal magnesium concentrations range between 1.0 and 5.0 mmol/l compared with serum magnesium concentrations of between 0.70 and 1.10 mmol/l, which provides a gradient favoring absorption [17]. The permeability of the paracellular pathway is regulated by proteins comprising the tight junction, including claudins, occludin, and zona-occludens-1[24]. Tight junction assembly and function can be modulated by a number of signaling molecules such as G proteins, phospholipase C, cAMP, protein kinase C, intracellular Ca\(^{2+}\), diacylglycerol that alter the phosphorylation state of the tight junctional proteins and the ionic permeability of the paracellular pathway [28].

When dietary magnesium intake is normal about 30% of intestinal magnesium absorption occurs via transcellular transport. This fraction increases when dietary magnesium intake is lower [9]. Transcellular magnesium absorption is mediated by TRPM6 and TRPM7 Mg\(^{2+}\) transporters (Fig. 1) that belong to the transient receptor potential melastatin superfamily of cationic channels. TRPM7 is ubiquitously expressed among tissues, whereas TRPM6 is found along the full length of the intestine (with the highest expression in the colon and caecum), along the kidney nephron (predominantly in distal convoluted tubules), in lung and testis tissues [23]. Both TRPM6 and TRPM7 are localized to the luminal membrane of the enterocytes and are permeable to both Mg\(^{2+}\) and Ca\(^{2+}\) but...
preferentially transport Mg\(^{2+}\) [29]. Mg\(^{2+}\) moves into the cell down the transmembrane electrochemical gradient, but the mechanism of the basolateral extrusion is unknown. Several publications have suggested that basolateral Mg\(^{2+}\) transport is coupled to the Na\(^{+}\), which intracellular concentration is maintained lower than in the blood via basolateral Na\(^{+}\), K\(^{-}\)-ATPase [19]. Factors controlling magnesium absorption are not well understood. Penner and Fleig (2007) have found that TRPM6 and TRPM7 are suppressed by elevated cytoplasmic free Mg\(^{2+}\) and Mg ATP, suggesting that cytosolic Mg\(^{2+}\) is an important regulator of channel function [15]. Intestinal Mg\(^{2+}\) absorption is altered by dietary intake of magnesium which effect can be attributed to changes in TRPM6 expression in the colon. It also, probably, depends on alterations in paracellular Mg\(^{2+}\) transport due to changes in the electrochemical gradient [6].

**RENA L REABSORPTION**

The kidney plays a crucial role in the maintenance of Mg\(^{2+}\) balance filtering approximately 2000-2400 mg of magnesium per day. Approximately 70 - 80% of total plasma Mg\(^{2+}\) (20-30% is protein bound) is available for glomerular filtration. Under normal conditions, 95-97% of filtered magnesium is reabsorbed in the renal tubules (Fig. 2) and only 3-5% is excreted in the urine i.e.~100 mg [3]. The kidneys may lower or increase magnesium excretion and reabsorption within a sizeable range: renal excretion of the filtered load may vary from 0.5 to 70%. The kidney is able to conserve magnesium during magnesium deprivation by reducing its excretion or rapidly increase Mg\(^{2+}\) excretion in cases of excess intake [20].

As shown in Figure 2, 10-25% of the filtered magnesium is absorbed in the proximal tubule. Although the exact mechanisms are not known, magnesium is believed to be absorbed via a paracellular pathway, facilitated by the increased intraluminal magnesium concentration. The majority of filtered Mg\(^{2+}\) is reabsorbed in the thick ascending limb of the loop of Henle (TAL) which accounts 50 - 70% of total reabsorption [12].

![Figure 2. Schematic overview of Mg\(^{2+}\) reabsorption along the nephron, transport pathways in the thick ascending limb of the loop of Henle and in the distal convoluted tubule.](image)

The passive paracellular transport in this segment is mediated by tight junction proteins claudin-16 and -19 and depends on transepithelial voltage gradient created by an active reabsorption of Na\(^{+}\). Na\(^{+}\) enters thick ascending loop cells via the apical Na\(^{+}\)-K\(^{-}\)-2Cl\(^{-}\) cotransporter (NKCC2). Basolateral Na\(^{+}\), K\(^{-}\)-ATPase plays a key role in this transport, maintaining a low intracellular Na\(^{+}\) concentration that provides
a favorable gradient for Na\(^+\) entry. K\(^-\) is recycled back into the luminal space via the renal outer medullary K\(^-\) (ROMK) channel and is involved in generating and maintaining a lumen-positive potential which in turn drives paracellular magnesium transport. Efflux of chloride (Cl\(^-\)) occurs through basolateral channel CLCKb.

Claudins are tight junction integral membrane proteins that are key regulators of the paracellular pathway. Claudin-16 is a highly negative charged protein. This negative charge contributes to the cationic selectivity of the reabsorptive paracellular pathway. The interaction between claudin-16 and claudin-19 is required for generating specific cation-permeable channels. Defects in either protein are causative for familial hypomagnesemia with hypercalciuria and nephrocalcinosis [7].

Some hormones such as parathyroid hormone (PTH), calcitonin, and antidiuretic hormone have been suggested to enhance Mg\(^{2+}\) transport in the TAL via the second messenger cAMP [18]. Magnesium transport in the thick ascending limb of the loop of Henle is also influenced by the calcium-sensing receptor (CaSR) in the basolateral membrane [8].

The ‘fine-tuning’ of Mg\(^{2+}\) reabsorption takes place along the distal convoluted tubule (DCT) as no reabsorption takes place beyond this segment. Approximately 10% of filtered Mg\(^{2+}\) is reabsorbed by an active transcellular transport via TRPM6 [4, 26]. The apical membrane potential in the DCT is negative, approximately -70 mV and is maintained by the apical voltage-gated K\(^-\) channel, Kv1.1 [5]. Because intracellular and extracellular Mg\(^{2+}\) concentrations are comparable, membrane potential provides the driving force for Mg\(^{2+}\) entry [26]. Basolateral Na\(^-\), K\(^+\)-ATP -ase and K\(^+\) recycling through Kir4.1 channel can alter Mg\(^{2+}\) reabsorption, regulating intracellular voltage needed for Mg\(^{2+}\) transport. At the basolateral membrane, extrusion of Mg\(^{2+}\) occurs against a steep electrochemical gradient via a recently identified magnesium/sodium exchanger SLC41A1 family [10]. Mg\(^{2+}\) reabsorption in the DCT is tightly regulated by plasma Mg\(^{2+}\) levels [6]. The acid-base status of an individual affects the body’s handling of Mg\(^{2+}\) through an alteration in levels of TRPM6 [13].

In the past decade, several hormones have been implicated in renal Mg\(^{2+}\) handling including Epidermal growth factor (EGF), estrogen, and insulin. Some recent studies provided evidence connecting a decreased Mg\(^{2+}\) concentration to insulin resistance and type 2 diabetes mellitus. Some studies demonstrated that insulin stimulates TRPM6 activity via increased plasma membrane abundance [27]. EGF and estrogen were termed magnesiotropic hormones considering their effect on both TRPM6 expression and channel function [2].

**CONCLUSION**

Mg\(^{2+}\) plays a vital physiological role in the body, and therefore control of plasma Mg\(^{2+}\) level is of major importance. Mg\(^{2+}\) homeostasis depends on three organs: the intestine, which determines Mg\(^{2+}\) uptake, bones that store Mg\(^{2+}\) and the kidneys, which are responsible for Mg\(^{2+}\) excretion.

**References:**