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Review

Magnesium deficiency: Does it have a role to play in cataractogenesis?

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ABSTRACT

Magnesium is one of the most important regulatory cation involved in several biological processes. It is important for maintaining the structural and functional integrity of vital ocular tissues such as lens. Presence of high magnesium content especially in the peripheral part of lens as compared to aqueous and vitreous humor has been observed. Magnesium plays significant role as a cofactor for more than 350 enzymes in the body especially those utilizing ATP. Membrane associated ATPase functions that are crucial in regulating the intracellular ionic environment, are magnesium-dependent. Moreover, the enzymes involved in ATP production and hydrolysis are also magnesium-dependent. Magnesium deficiency by interfering with ATPase functions causes increased intracellular calcium and sodium and decreases intracellular potassium concentration. Furthermore, magnesium deficiency is associated with increased oxidative stress secondary to increased expression of inducible nitric oxide synthase and increased production of nitric oxide. Thus the alterations in lenticular redox status and ionic imbalances form the basis of the association of magnesium deficiency with cataract. In this paper we review the mechanisms involved in magnesium homeostasis and the role of magnesium deficiency in the pathogenesis of cataract.

1. Introduction

Magnesium is an important cation that plays significant role as a cofactor for more than 350 enzymes in the body, especially those utilizing high energy phosphate bonds such as ATPases (Wolf and Cittadini, 2003; Yang et al., 2006; Cowan, 2002). Besides being involved in maintaining the genomic stability, processes of synthesis, transcription, and translation (Yang et al., 2006; Vernon, 1988; Sreedhara and Cowan, 2002), it also regulates activity of several ion channels. Magnesium homeostasis is closely linked with calcium, sodium and potassium homeostasis and therefore any disturbances in magnesium homeostasis are bound to be associated with calcium, sodium and potassium homeostasis and vice versa. Clearly, the consequences of disturbances in magnesium homeostasis may seriously affect the cellular and molecular functions and may form the basis of several pathological conditions. Ocular tissue especially the lens is as susceptible to changes in magnesium homeostasis as any other organ in the body. The structural and functional integrity of the lens which is of primary importance in transmitting the light to retina largely depends on the maintenance of intracellular and extracellular ionic homeostasis. In this review we summarize the knowledge available from currently available literature with regards to the mechanisms of magnesium homeostasis and association of magnesium deficiency states with cataract. Literature search was made using Pubmed search engine. Several key word like magnesium, calcium, ocular, ophthalmic, cataract were used. Full texts of all research papers in English and Russian language were read and abstracts in English language were read for those published in other languages. A total of 114 references are included in this paper published during 1960–2011.

2. Magnesium homeostasis and its regulation

Regulation of magnesium homeostasis involves maintenance of normal distribution and total magnesium contents in different body compartments. Physiological homeostatic mechanisms of the body regulate the body magnesium contents and distribution unless the pathological conditions bring about alterations in normal homeostasis.

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2.1. Normal body magnesium contents and distribution

Adult human body contains about 15 mmol of magnesium per kg bodyweight. About 50% of total pool of magnesium is in the bones, less than 50% is in the muscles and soft tissue (about 28% is in striated muscles) (Moskalev, 1985; Okazaki, 1988; Wacker and Vallee, 1958). About 1% of magnesium is in extracellular fluid and about 0.3% is in serum (in the ionized form) (Revúsová and Dzúrik, 1984) with a physiological range of 0.75–1 mmol/l. One third of serum magnesium is bound to plasma proteins, preferentially to albumin and to a lesser extent to globulins (Kroll and Elin, 1985; Lau et al., 1985). In healthy individuals average concentration of serum magnesium is rather stable, whereas concentration of total magnesium is affected by circadian variations and the lowest values are observed between 6:00 and 10:00 in the morning (Elin et al., 1994; Graham et al., 1960).

2.2. Dietary magnesium requirements

The usual diet quite varies in magnesium content and provides 2–7.5 mg magnesium/kg body weight (Vormann, 2003). During recent years dietary reference intakes for magnesium have been revised and current recommended intakes of magnesium for adults are between 300 and 420 mg/day. Normal American or European diet may maintain normal level of magnesium in the body (Rude, 1998; Spasov, 2000) and dietary magnesium deficiency occurs rather rarely. However, rapid growth and pubertal period as well as pregnancy and lactation require higher magnesium intake (Mitrović and Jovanović, 2002).

2.3. Physiological basis of the regulation of magnesium homeostasis

The extracellular magnesium level depends on the balance between intestinal absorption and renal excretion. Within physiological ranges, decrease in magnesium intake is counterbalanced with increase in intestine magnesium absorption and decrease in renal magnesium excretion.

Gastrointestinal tract absorbs not more than 30% of ingested magnesium and this absorption primarily occurs in the ileum and colon. In severe magnesium depletion, significantly more magnesium can be absorbed. Absorption involves passive (paracellular) and active (transcellular) transport mechanisms (Quamme et al., 1994).

Kidney is the main regulator of magnesium homeostasis. Decrease or increase in magnesium intake by individuals with normal renal function results in decreased or increased urinary excretion of magnesium respectively (Shils, 1969; Heaton, 1969). However, there are daily and circadian changes of this parameter (Johansson, 1979; Sjögren et al., 1987). Control of magnesium homeostasis mainly occurs at the level of nephron in kidneys. About 80% of total magnesium is filtered through the glomerular membrane (Brunette and Crochet, 1975; Le Grimellec et al., 1975). At the rate of glomerular filtration of 125 ml/min the amount of filtered magnesium is about 140 mmol per day. Kidney reabsorbs about 80–99% of this filtered magnesium and 1–20% is excreted in urine (Quamme et al., 1994). Proximal tubules reabsorb 5–15%, the thick ascending limb of Henle's loop absorbs 70–80%, and the distal tubule reabsorbs about 5–10% of filtered magnesium. Although the distal tubule reabsorbs only 10% of magnesium filtered through the glomerule, this is a significant amount, representing about 60–70% of magnesium entering this segment from the Henle's loop (Quamme and de Rouffignac, 2000). Only insignificant amount of magnesium is reabsorbed in collecting tubules so that the tubular segments of this part of nephron play an important role in determining final urinary excretion of magnesium (Quamme and de Rouffignac, 2000; Quamme, 1989; Quamme et al., 2000). Magnesium reabsorption in the loop occurs within the cortical thick ascending limb by passive means driven by the transepithelial voltage through the paracellular pathway.

The thick ascending limb of Henle's loop mediates transcellular reabsorption of NaCl while generating a lumen-positive voltage that drives passive paracellular reabsorption of divalent cations (Ca^{2+} and Mg^{2+}). Disturbance of paracellular reabsorption leads to divalent cations wasting in patients with the rare inherited disorder of familial hypercalciuric hypomagnesemia with nephrocalcinosis. Recent work has shown that the claudin family of tight junction proteins (claudin-16/paracellin-1 and claudin-19) form paracellular pores and determine the ion selectivity of paracellular permeability (Cole and Quamme, 2000; Günzel and Yu, 2009; Haisch et al., 2011).

Unlike the thick ascending limb of the loop of Henle, magnesium reabsorption in the distal tubule is transcellular and active in nature (Quamme and de Rouffignac, 2000). Critical role in this process belongs to the members of the melastatin-related subfamily of transient receptor potential (TRP) ion channels, TRPM6 and TRPM7, gatekeepers of human magnesium metabolism. Recently, genetic studies in patients with primary hypomagnesaemia and secondary hypocalcaemia have identified TRPM6 as the first component involved directly in epithelial magnesium reabsorption. TRPM7, the closest homologue of TRPM6, has a central role in Mg^{2+} uptake in vertebrate cells since TRPM7-deficient cells become Mg^{2+} deficient and are not viable. TRPM7 has been characterized functionally as a constitutively active ion channel permeable for a variety of cations including calcium and magnesium and regulated by intracellular concentrations of magnesium and/or magnesium–nucleotide complexes. Both proteins share the unique feature of cation channels fused to serine/threonine kinase domains (Schlingmann et al., 2007; Chubanov and Gudermann, 2005).

Many hormones and nonhormonal factors influence renal magnesium reabsorption to variable extent in the cortical thick ascending limb and distal tubule. Moreover, nonhormonal factors may have important implications on hormonal controls of renal magnesium conservation. Parathyroid hormone, calcitonin, glucagon, and antidiuretic hormone act through a common second messenger, adenosine 3′,5′-cyclic monophosphate, to limit magnesium excretion by enhancing active magnesium transport in the cortical thick ascending limb (Quamme and de Rouffignac, 2000; Quamme et al., 2000; Dai et al., 2001). Adaptation of magnesium transport with dietary magnesium restriction or excess dietary intake occurs in both the cortical thick ascending limb and distal tubule. The identification of an extracellular Ca^{2+}/Mg^{2+}-sensing receptor located on the peritubular side of the cortical thick ascending limb and distal tubule cells explains this phenomenon. Loop diuretics, such as furosemide and bumetanide, diminish salt absorption in the cortical thick ascending limb whereas the distally acting diuretics, amiloride and chlorothiazide stimulate magnesium reabsorption within the distal convoluted tubule. Finally, metabolic acidosis, potassium depletion or phosphate restriction can diminish magnesium reabsorption within the loop and distal tubule (Quamme and de Rouffignac, 2000; Quamme et al., 2000; Dai et al., 2001). Magnesium deficiency may arise together with and contribute to the persistence of potassium deficiency and cases of magnesium deficiency accompanying the magnesium-dependent or -independent potassium deficiency are not uncommon among the general population.

2.4. Disturbances of magnesium homeostasis: causes and associated diseases

Magnesium deficiency appears as a result of altered functional state of the body, in some pathological conditions such as diabetes