Magnesium Handling in the Kidney

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Magnesium is a divalent cation that fills essential roles as regulator and cofactor in a variety of biological pathways, and maintenance of magnesium balance is vital to human health. The kidney, in concert with the intestine, has an important role in maintaining magnesium homeostasis. Although micropuncture and microperfusion studies in the mammalian nephron have shone a light on magnesium handling in the various nephron segments, much of what we know about the protein mediators of magnesium handling in the kidney have come from more recent genetic studies. In the proximal tubule and thick ascending limb, magnesium reabsorption is believed to occur primarily through the paracellular shunt pathway, which ultimately depends on the electrochemical gradient setup by active sodium reabsorption. In the distal convoluted tubule, magnesium transport is transcellular, although magnesium reabsorption also appears to be related to active sodium reabsorption in this segment. In addition, evidence suggests that magnesium transport is highly regulated, although a specific hormonal regulator of extracellular magnesium has yet to be identified.

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WHOLE BODY MAGNESIUM HOMEOSTASIS

In its roles as both a direct allosteric modulator and a cofactor in complex with ATP, magnesium is essential for the normal function of a multitude of proteins, including a number of enzymes involved in glycolysis and oxidative phosphorylation.[1,2] Magnesium also plays a direct role in the stabilization of nucleotides, and both intracellular and extracellular magnesium concentrations have been shown to modulate the activity of ion channels.[3-5] Accordingly, perturbations of magnesium balance are associated with systemic signs and symptoms. In particular, magnesium disturbances are associated with tetany, muscle fasciculations, and weakness, especially at serum levels less than 1.2 mg/dL.[6] In addition to disruption of the aforementioned processes, symptoms of hypomagnesemia may be related to hypoparathyroidism and hypocalcemia that arise secondarily from reduced parathyroid hormone (PTH) secretion.[7]

Under normal physiologic conditions, the serum magnesium is held relatively constant between 1.6 and 2.3 mg/dL.[8] The overwhelming majority (approximately 99%) of magnesium in the body is either stored in bone or within cells.[8] Bone contains about half of total body magnesium, and bone magnesium seems to correlate well with serum magnesium across species, including man.[9] While magnesium is much higher in cells than serum, the free magnesium ion concentrations are very similar due to buffering by proteins and ATP and sequestration in organelles such as mitochondria.[10,11] Due to the relatively negative intracellular environment, magnesium entrance into the cell is passive, but extrusion of magnesium out of the cell occurs against an electric gradient.[10] Consequently, transcellular magnesium transport is likely to be active.

Magnesium balance is achieved by the concerted actions of the intestine and kidneys. Indeed, net kidney excretion of magnesium has a linear relationship to net intestinal absorption across a wide range of magnesium intakes.[12,13] A normal daily magnesium intake averages around 300 mg, of which approximately 50% is absorbed by the intestine.[14] Net intestinal magnesium absorption follows a curvilinear rise as dietary magnesium intake increases, revealing a hyperbolic, saturable increase in absorption predominating at lower lumen magnesium concentrations and a linear, nonsaturable rise which dominates with normal magnesium intake.[12] These two separate processes likely correspond to active and passive transport, respectively.

Recent segmental analysis of intestinal magnesium transport in mice suggests that, in contrast to calcium reabsorption, the majority of active magnesium absorption occurs in the later intestinal segments.[15] In these segments, mRNA expression of the magnesium channel, melastatin-related transient receptor potential cation channel 6 (TRPM6), is highest in humans and mice.[15] Homozygous loss-of-function mutations in the magnesium channel TRPM6 cause the magnesium wasting disorder hypomagnesemia with secondary hypocalcemia (HSH), a disorder in which intestinal malabsorption of magnesium occurs alongside a kidney magnesium leak.[16,17] Thus, TRPM6 is likely the major mediator of active magnesium transport in the distal colon. The role of TRPM6 in kidney magnesium handling will be reviewed further in the sections below.

The paracellular transport properties of a given epithelial layer are determined by the electrochemical gradients as well as the protein composition of the most apical structure of the junctional complex, the tight junction. Namely, the claudin family of tetraspan proteins forms barrier or charge- and size-selective pores at the tight junction, the expression of which varies between tissue and cell type (for an extensive review, see the study by Hou and colleagues[18]). The small intestine has a lower transepithelial resistance (TER) and higher permeability to sodium over chloride (P_{Na}/P_{Cl}) than the colon, corresponding to the

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site of highest expression of cation-selective claudin isoforms such as claudin-12 and claudin-15.[19-22] Notably, the transepithelial potential of the small intestine is lumen negative, suggesting that paracellular magnesium transport is primarily driven by its concentration gradient.[23,24] Magnesium absorption in the proximal intestine has a linear relationship with luminal magnesium concentration and exceeds that of the distal intestine at higher magnesium concentrations.[15] Together, these data suggest that the bulk of paracellular magnesium absorption occurs in the small intestine.

As intestinal magnesium absorption has a direct relationship to dietary magnesium intake, its role in the regulation of serum magnesium is not clear. The kidney rapidly responds to changes in serum magnesium, and infusion studies reveal that urine magnesium acutely increases as serum magnesium increases during a 30-minute infusion.[25] This reveals a striking role for the kidney in maintaining extracellular magnesium concentrations (Fig. 1). The physiology of kidney magnesium transport and its regulation is detailed in the sections below.

CLINICAL SUMMARY

- Magnesium is an important mineral for human health, and levels are kept constant primarily by the gastrointestinal tract and kidneys.
- The proximal tubule reabsorbs 10%-20% of filtered magnesium.
- The thick ascending limb is responsible for the majority of kidney magnesium reabsorption, and regulation of this transport occurs in large part by modulation of tight junction permeability.
- The distal convoluted tubule reabsorbs 5% of magnesium through a transcellular pathway that is disrupted in a number of tubulopathies.

MAGNESIUM TRANSPORT IN THE KIDNEY

Serum magnesium circulates in both soluble and protein bound forms. The pool of magnesium that is bound by proteins in human serum averages 32%.[28] The remainder of serum magnesium is in its ionized form (55%) or within soluble complexes with anions like phosphate and citrate (13%) and is ultrafilterable.[8,28] Despite a mere 1% of total body magnesium being present in the extracellular fluid, about one-tenth of total body magnesium is filtered by the kidney in a 24-hour period.[8]

Proximal Tubule

The proximal tubule (PT) is the site of the majority of sodium, potassium, chloride, and calcium reabsorption in the nephron, yet only about 10%-20% of filtered magnesium is reabsorbed in this segment.[8,29] The PT has a high permeability to water and small ions such as sodium and chloride. These properties allow active sodium reabsorption and its concomitant electrochemical gradients to drive isosmotic reabsorption of many solutes.[8] Micropuncture studies in rats report that magnesium, far from being isosmotic, becomes concentrated to a tubular fluid-to-ultrafilterable magnesium ratio of about 1.65 in the late PT,[30] and the permeability of the PT to magnesium is so low that significant transport only occurs at a tubular fluid to ultrafilterable above 1.9.[31] Experimental extracellular fluid volume expansion results in the near absence of net PT magnesium transport.[32] The molecular mediator of magnesium reabsorption has not yet been identified, although it is often speculated that magnesium reabsorption occurs through a paracellular shunt. This is in part because PT magnesium reabsorption has an unsaturable, linear relationship with the luminal magnesium concentration.[27] Claudin-2 is a cation-selective claudin isoform that greatly increases sodium permeability (P_{Na}) when overexpressed in kidney epithelial cells.[33] Due to its high expression in the PT compared with other cation-selective isoforms,[34-37] it is a reasonable candidate to mediate PT magnesium transport. Deletion of the claudin-2 gene in mice results in reduced reabsorption of water and solutes in isolated PT segments but does not result in an increased fractional excretion of magnesium (FE_{Mg}).[38] It is certainly possible that, given the diminished role of PT magnesium reabsorption compared with calcium, a PT magnesium leak in claudin-2 knockout mice might be negated by efficient compensation in the downstream nephron. While claudin-10 is also highly expressed in the PT, there are multiple splice variants of claudin-10 with differing charge selectivity and tissue expression, and the anion-selective splice variant claudin-10a is the predominant isoform expressed in the PT of mice.[39,40] Studies in rats reveal that neonatal animals reabsorb about two-thirds of magnesium in the PT, similar to reabsorption of sodium and calcium in this segment.[41] Interestingly, claudin-6 and claudin-9 are highly expressed in the PTs of neonatal mice but not in adult mice.[42-44] However, both claudin isoforms increase TER and reduce cation permeability when overexpressed in kidney epithelial cells.[45] Thus, the molecular facilitators of PT magnesium reabsorption in adult and neonatal mammals remain a mystery.

Thick Ascending Limb

The thick ascending limb of the loop of Henle (TAL) is the predominant site of magnesium reabsorption in the kidney, reabsorbing approximately 60% of filtered magnesium.[27,30] Unlike the PT, the TAL has a very low permeability to water. Electroneutral transport by the Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) in the TAL is responsible for diluting the tubular fluid and creating the corticomedullary osmotic gradient. At the apical membrane, the electrogenic potassium channel ROMK allows the potassium transported into the cell by NKCC2 to return to the urinary space. Simultaneously, the basolateral chloride channel ClC-Kb allows reabsorbed chloride to enter the bloodstream. These processes combine to produce a large lumen-positive transepithelial voltage.[46] Studies in mice suggest that the majority of magnesium and calcium reabsorption occurs in the cortical