Mechanism of Hypokalemia in Magnesium Deficiency

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ABSTRACT

Magnesium deficiency is frequently associated with hypokalemia. Concomitant magnesium deficiency aggravates hypokalemia and renders it refractory to treatment by potassium. Herein is reviewed literature suggesting that magnesium deficiency exacerbates potassium wasting by increasing distal potassium secretion. A decrease in intracellular magnesium, caused by magnesium deficiency, releases the magnesium-mediated inhibition of ROMK channels and increases potassium secretion. Magnesium deficiency alone, however, does not necessarily cause hypokalemia. An increase in distal sodium delivery or elevated aldosterone levels may be required for exacerbating potassium wasting in magnesium deficiency.

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Hypokalemia is among the most frequently encountered fluid and electrolyte abnormalities in clinical medicine. The concentration of potassium (K^+)in the serum is a balance among intake, excretion, and distribution between the extra- and intracellular spaces.[1] Accordingly, hypokalemia may be caused by redistribution of K^+ from serum to cells, decreased dietary intake, or excessive loss of K^+ from the gastrointestinal track or from the kidney. Understandably, hypokalemia from excess renal or gastrointestinal loss or reduced intake would likely be associated with loss and deficiency of other ions. It is estimated that more than 50% of clinically significant hypokalemia has concomitant magnesium deficiency. Clinically, combined K^+ and magnesium deficiency is most frequently observed in individuals receiving loop or thiazide diuretic therapy.[1] Other causes include diarrhea; alcoholism; intrinsic renal tubular transport disorders such as Bartter and Gitelman syndromes; and tubular injuries from nephrotoxic drugs, including aminoglycosides, amphotericin B, cisplatin, *etc.* Concomitant magnesium deficiency has long been appreciated to aggravate hypokalemia.[2] Hypokalemia associated with magnesium deficiency is often refractory to treatment with K^+. Co-administration of magnesium is essential for correcting the hypokalemia. The mechanism of hypokalemia in magnesium deficiency, however, remains unexplained. Here, we review existing literature on the subject to provide better understanding of the mechanism. Because of space limitations, this review cites review articles in lieu of many original publications.

Previous articles suggested that impairment of Na-K-ATPase caused by magnesium deficiency contributes to K^+ wasting.[3,4] Magnesium deficiency impairs Na-K-ATPase, which would decrease cellular uptake of K^+.[3] A decrease in cellular uptake of K^+, if it occurs along with increased urinary or gastrointestinal excretion, would lead to K^+ wasting and hypokalemia. Little K^+ is excreted by the gastrointestinal tract normally; therefore, hypokalemia in magnesium deficiency is likely associated with enhanced renal K^+ excretion. To support this idea, Baehler *et al.*[5] showed that administration of magnesium decreases urinary K^+ excretion and increases serum K^+ levels in a patient with Bartter disease with combined hypomagnesemia and hypokalemia. Similarly, magnesium replacement alone (without K^+) increases serum K^+ levels in individuals who have hypokalemia and hypomagnesemia and receive thiazide treatment.[6] Magnesium administration decreased urinary K^+ excretion in these individuals (Dr. Charles Pak, personal communication, UT Southwestern Medical Center at Dallas, July 13, 2007). Moreover, magnesium infusion decreases urinary K^+ excretion in normal individuals.[7]

K^+ is freely filtered at the glomerulus. Most of the filtered K^+ is reabsorbed by the proximal tubule and the loop of Henle. K^+ secretion occurs in the late distal convoluted tubule and the cortical collecting duct, which contributes in large part to urinary K^+ excretion.[1] Kamel *et al.*[8] addressed the tubular site of action of magnesium by measuring the transtubular K^+ concentration gradient (TTKG). The TTKGprovides an indirect

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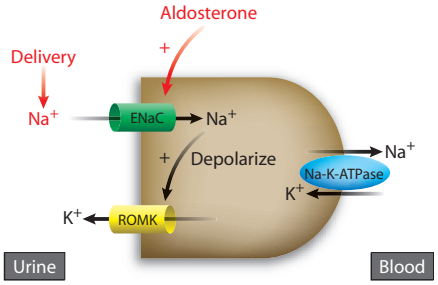

Figure 1. K^+ secretion in the distal nephron. K^+ is taken up into cells across the basolateral membrane *via* Na-K-ATPases (blue oval) and secreted into luminal fluid *via* apical ROMK channels (yellow cylinder). Sodium (Na^+) reabsorption *via* ENaC (green cylinder) depolarizes the apical membrane potential and provides the driving force for K^+ secretion (indicated by dotted line and plus sign). Thus, increased Na^+ delivery (indicated by black line) would stimulate K^+ secretion. Aldosterone increases sodium reabsorption *via* ENaC to stimulate K^+ secretion (indicated by red line).

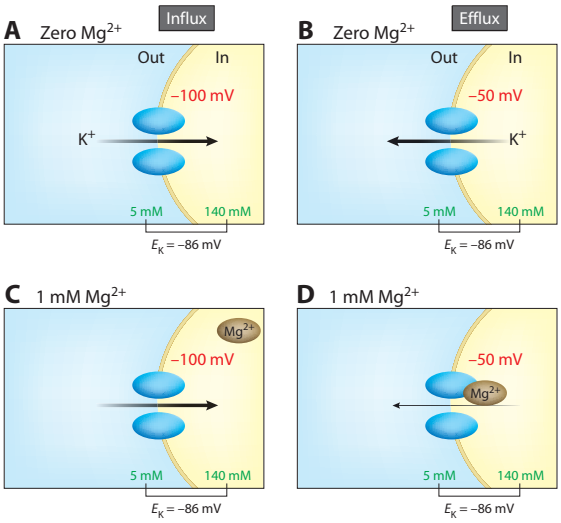

Figure 2. Mechanism for intracellular magnesium to decrease K^+ secretion. A ROMK channel in the apical membrane of distal nephron is depicted. (A and B) At zero intracellular Mg^{2+}, K^+ ions move in or out of cell through ROMK channels freely depending on the driving force (*i.e.*, not rectifying). At intra- and extracellular K^+ concentrations of 140 and 5 mM, respectively, the chemical gradient drives K^+ outward. An inside-negative membrane potential drives K^+ inward. Inward and outward movement of K^+ ions reach an equilibrium at −86 mV (*i.e.*, equilibrium potential [E_K] = $-60 \times \log \frac{140}{5}$). When membrane potential is more negative than E_K (*e.g.*, −100 mV, a condition that rarely occurs in the apical membrane of distal nephron physiologically), K^+ ions move in (influx; see A). Conversely, at membrane potential more positive than E_K (*e.g.*, −50 mV, a physiologic relevant condition), K^+ ions move out (see B). (C and D) At the physiologic intracellular Mg^{2+} concentration (*e.g.*, 1 mM), ROMK conducts more K^+ ions inward than outward (*i.e.*, inward rectifying). This is because intracellular Mg^{2+} binds ROMK and blocks K^+ efflux (secretion; see D). Influx of K^+ ions displaces intracellular Mg^{2+}, allowing maximal K^+ entry (see C). This unique inward-rectifying property of ROMK places K^+ secretion in the distal nephron under the regulation by intracellular Mg^{2+}. Note that, though inward conductance is greater than outward, K^+ influx (i.e., reabsorption) does not occur because of membrane potential more positive than EK.

reflection of K^+ secretion in the distal nephron. The authors found that magnesium infusion (but not ammonium chloride infusion to correct metabolic alkalosis) reduced urinary K^+ excretion and decreased TTKG in four of six patients with Gitelman disease and hypokalemia, hypomagnesemia, and metabolic alkalosis. Thus, magnesium replacement prevents renal K^+ wasting, at least in part, by decreasing secretion in the distal nephron. Previous micropuncture studies also confirmed that magnesium decreases distal K^+ secretion.[9,10]

What is the cellular mechanism for the decrease in K^+ secretion by magnesium? In the late distal tubular and cortical collecting duct cells, K^+ is taken up into cells across the basolateral membrane *via* Na-K-ATPases and secreted into luminal fluid *via* apical K^+ channels. Two types of K^+ channels mediate apical K^+ secretion: ROMK and maxi-K channels. ROMK is an inward-rectifying K^+ channel responsible for basal (non–flow stimulated) K^+ secretion.[11] Inward rectification means that K^+ ions flow in the cells through ion channels more readily than out.[12] Sodium (Na^+) reabsorption *via* epithelial Na^+ channel (ENaC) depolarizes the apical membrane potential, which provides the driving force for K^+ secretion. Aldosterone increases sodium reabsorption *via* ENaC to stimulate K^+ secretion (Figure 1). Maxi-K channels are responsible for flow-stimulated K^+ secretion (data not shown). Inward rectification of ROMK results when intracellular Mg^{2+} binds and blocks the pore of the channel from the inside, thereby limiting outward K^+ flux (efflux). Inward K^+ flux (influx) would displace intracellular Mg^{2+} from the pore and release the block (Figure 2). The concentration of intracellular Mg^{2+} required for inhibition of ROMK depends on membrane voltage and the extracellular concentration of K^+.[13] At the physiologic extracellular K^+ and apical membrane potential in the distal nephron, the effective intracellular concentration of Mg^{2+} for inhibiting ROMK ranges from 0.1 to 10.0 mM, with the median concentration at approximately 1.0 mM.[13] The intracellular Mg^{2+} concentration is estimated at 0.5 to 1.0 mM.[14] Thus, intracellular Mg^{2+} is a critical determinant of ROMK-mediated K^+ secretion in the distal nephron. Changes in intracellular Mg^{2+} concentration over the physiologic-pathophysiologic range would significantly affect K^+ secretion.

Magnesium is the most abundant divalent cation in the body. Approximately 60% of magnesium is stored in bone, another 38% is intracellular in soft tissues, and only approximately 2% is in extracellular fluid including the plasma. The

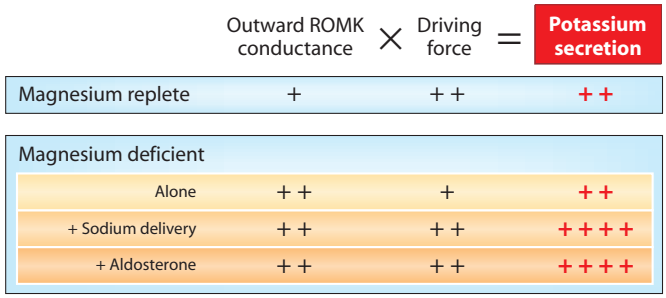

Figure 3. Summary of effects of intracellular magnesium and driving force on K^+ secretion.

cytosol is the largest intracellular compartment for Mg^{2+}. The cellular Mg^{2+} concentration is estimated between 10 to 20 mM. In the cytosol, Mg^{2+} ions mainly form complexes with ATP and, to a smaller extent, with other nucleotides and enzymes. Only approximately 5% of Mg^{2+} (0.5 to 1.0 mM) in the cytosol is free (unbound).[14] The degree of exchange of Mg^{2+} between tissues and plasma varies greatly. It was shown in kidney and heart that 100% of intracellular Mg^{2+} can exchange with plasma within 3 to 4 h.[15] In contrast, only approximately 10% of magnesium in brain and 25% in skeletal muscle can exchange with plasma, and the equilibrium occurs after ≥16 h. The basis for the differences is not known. The intracellular concentration of free Mg^{2+} in renal tubules in magnesium-deficiency states has not been measured. Nevertheless, these results support the idea that intracellular Mg^{2+} in renal tubules falls readily during magnesium deficiency. Consistent with the rapid exchange between heart and plasma, Mg^{2+} depletion causes profound adverse effects on myocardium.[16]

Several genetic disorders of magnesium homeostasis have magnesium wasting without concomitant K^+ wasting.[17] These include familial hypomagnesemia with hypercalciuria and nephrocalcinosis, caused by mutations of a tight-junction protein Paracellin-1 in the thick ascending limb of Henle's loop, and hypomagnesemia with secondary hypocalcemia, caused by mutations of the magnesium channel TRPM6.[18,19] In these genetic diseases of magnesium transporter disorder[17–19] and experimental models of isolated dietary magnesium deficiency,[4,10] serum K^+ levels and urinary K^+ excretion are normal. How do these findings reconcile with the proposed model that lowering intracellular Mg^{2+} increases ROMK-mediated K^+ secretion in the distal tubules? One reason for the lack of significant hypokalemia and K^+ wasting in isolated magnesium deficiency is related to the impairment of Na-K-ATPase. Decreased cellular K^+ uptake in the muscle and the kidney would tend to maintain serum K^+ levels but decrease renal K^+ secretion[4,10]; therefore, additional factors are needed for promoting renal K^+ excretion. Another reason is related to the fact that ROMK channels in the apical membrane of distal tubules also play an important role in regulating membrane potential.[11] An increase in the K^+ secretion would hyperpolarize membrane potential (as a result of loss of intracellular positive charges), which decreases the driving force for outward K^+ flux and ultimately limits the total amount of K^+ secretion; therefore, a mere increase in ROMK activity from a low intracellular Mg^{2+} may not be sufficient to cause a significant K^+ wasting. Additional factors that would provide an unabating driving force for K^+ secretion (*i.e.*, prevent apical membrane hyperpolarization), such as an increase in distal sodium delivery and elevated aldosterone levels, are important for exacerbating K^+ wasting in magnesium deficiency (Figure 3). One or both factors are present in diuretics therapy, diarrhea, alcoholism, Bartter and Gitelman syndromes, and tubular injuries from nephrotoxic drugs.

Magnesium and K^+ are the two most abundant intracellular cations. Because of their predominant intracellular distribution, deficiency of these ions is underrecognized. Both magnesium and K^+ are critical for stabilizing membrane potential and decreasing cell excitability.[16] Magnesium deficiency will not only exacerbate K^+ wasting but also aggravate the adverse effects of hypokalemia on target tissues.[16] Recognition of concomitant magnesium deficiency and early treatment with magnesium are imperative for effective treatment and prevention of complications of hypokalemia.

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DISCLOSURES

None.

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