Renal magnification by EGF*

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A paper recently published by Groenestege and colleagues [8] used positional cloning to determine the cause of a rare inherited magnesium-wasting syndrome, autosomal recessive renal hypomagnesemia. The results showed that certain mutations in the epidermal growth factor (EGF) gene cause this disease. This suggests, perhaps surprisingly, that EGF and its receptor comprise a previously unrecognized signaling pathway in the human kidney that participates importantly in magnesium homeostasis. The EGF gene is highly expressed along the distal convoluted tubule (DCT), an important site for regulating urinary magnesium excretion. A portion of the extracellular domain can be cleaved to form the 53-amino-acid hormone, EGF; it is believed that cleavage occurs preferentially at the basolateral surface, leading to increased apparent EGF abundance at the apical membrane. In the DCT, EGF binds to receptors at the basolateral surface, making basolateral EGF expression a necessary prerequisite for signaling. The gene defect that causes autosomal recessive renal hypomagnesemia appears to disrupt trafficking of pro-EGF to the basolateral membrane, thereby impeding its signaling capability. The results also showed that EGF stimulates magnesium transport by TRPM6 (transient receptor potential cation channel, subfamily M, member 6), a channel that is expressed at the apical membrane of DCT cells and appears to be a primary path for apical magnesium entry. Interestingly, the investigators also corroborated previous reports that cancer patients treated with an antagonist of the EGF receptor, cetuximab, develop renal magnesium wasting and hypomagnesemia, emphasizing the significance of EGF in maintaining magnesium balance in humans.

Magnesium homeostasis in health and disease

Magnesium is the second most abundant intracellular cation; it is essential for cellular homeostasis and enzyme activity, so the renal ability to conserve magnesium is great. Approximately 80% of plasma magnesium is filtered; 10–15% of filtered magnesium is reabsorbed along the proximal tubule, 55–60% along the thick ascending limb and 5–10% along the DCT [17]. Although hypomagnesemia can result from gastrointestinal losses, renal magnesium wasting is usually involved. Hypomagnesemia occurs in ~12% of hospitalized patients [22], ~17% of patients with heart failure [13] and up to 60% of patients in intensive care [4]. Signs of severe hypomagnesemia resemble signs of hypocalcemia and include tetany, generalized convulsions and, occasionally, cardiac arrhythmias. Milder symptoms are often nonspecific, but troubling, and include malaise and paresthesias, often accompanied by hypokalemia and hypocalcemia. Magnesium deficiency predisposes to potassium loss, usually in states of hyperaldosteronism. Intracellular magnesium blocks potassium movement through potassium channels, so cellular magnesium depletion may enhance potassium channel activity [10]. Other factors, however, such as nutritional deficiency, diuretic use and increased aldosterone, often accompany combined hypokalemia and hypomagnesemia and probably contribute [5].

Magnesium reabsorption by the kidney

The molecular basis of magnesium transport is only recently being elucidated, and our picture of renal magnesium transport pathways remains incomplete. Knowledge has been gained largely when genes that cause rare diseases of magnesium wasting have been identified. Mutations in claudin-16 (also called paracellin) and claudin-19, proteins expressed along the thick ascending limb, cause hereditary magnesium wasting with nephrocalcinosis (see Figure 1) [11,19]. Along this segment, magnesium is reabsorbed across the paracellular pathway [9], driven by the transepithelial voltage. Mutations in transport proteins expressed along the DCT, including the thiazide-sensitive Na–Cl cotransporter...
Implications for clinical practice

Hypomagnesemia commonly complicates treatment with a number of therapeutic agents, including the calcineurin inhibitors cyclosporine and tacrolimus, antineoplastic drugs, such as cisplatin, the antifungal, amphotericin B, the antibiotics, gentamicin and pentamidine, the antiviral, ribavirin and the antiretroviral, foscarnet. Cisplatin, for example, frequently causes magnesium wasting with hypocalciuria and hypokalemia, resembling Gitelman syndrome [12,16], a disease caused by defective electroneutral Na–Cl cotransport in the DCT. Calcineurin inhibitor use is accompanied by hypomagnesemia in as many as 40% of cases (especially with tacrolimus), but it is usually associated with hypercalciuria. This resembles the hereditary syndrome of hypomagnesemia with hypercalciuria and nephrocalcinosis, suggesting a defect in TAL function. In fact, cyclosporin reduces the abundance of claudin-16 in rats [3], mimicking the phenotype of the inherited disease, although defects in other nephron segments also occur [15]. The work described by Bindels and
colleagues [8] not only suggests an explanation for a well-documented and troubling side effect of anti-EGF receptor agents, but also suggests that EGF participates in a novel autocrine or paracrine-signaling pathway in the distal nephron; the physiological relevance of this pathway remain to be elucidated.

An understanding of sites and mechanisms of disrupted magnesium transport induced by therapeutic agents suggests rational approaches to prevention and treatment. When hypomagnesemia is accompanied by hypokalemia and hypocalciuria, resembling Gitelman syndrome, amiloride treatment effectively improves hypomagnesemia and hypokalemia [21]. The identification that EGF receptor antagonists also cause a defect in DCT function suggests that the same approach might be effective. When hypomagnesemia is accompanied by hypercalciuria, the primary defect more likely lies in the TAL, and different approaches may be necessary. None of this should distract, however, from the most important aspect of drug-induced hypomagnesemia; unless the problem is recognized and plasma magnesium levels are measured, this common, morbid and often treatable disorder will be missed.

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References

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