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Inherited and Acquired Disorders of Magnesium Homeostasis

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Abstract

Purpose of review—Magnesium (Mg^{2+}) imbalances are frequently overlooked. Hypermagnesemia usually occurs in preeclamptic women after Mg^{2+} therapy or in end-stage renal disease patients, while hypomagnesemia is more common with a prevalence of up to 15% in the general population. Increasing evidence points towards a role for mild to moderate, chronic hypomagnesemia in the pathogenesis of hypertension, type 2 diabetes mellitus, and metabolic syndrome.

Recent findings—The kidneys are the major regulator of total body Mg^{2+} homeostasis. Over the last decade the identification of the responsible genes in rare genetic disorders has enhanced our understanding of how the kidney handles Mg^{2+}. The different genetic disorders and medications contributing to abnormal Mg^{2+} homeostasis are reviewed.

Summary—As dysfunctional Mg^{2+} homeostasis contributes to the development of many common human disorders, serum Mg^{2+} deserves closer monitoring. Hypomagnesemic patients may be asymptomatic or may have mild symptoms. In severe hypomagnesemia patients may present with neurological symptoms such as seizures, spasms or cramps. Renal symptoms include nephrocalcinosis and impaired renal function. Most conditions affect tubular Mg^{2+} reabsorption by disturbing the lumen-positive potential in the thick ascending limb or the negative membrane potential in the distal convoluted tubule.

Keywords

Magnesium; kidney; physiology; tubule; nephron

Introduction

Magnesium (Mg^{2+}) is a frequently neglected electrolyte despite being the second most abundant intracellular cation(1). Mg^{2+} plays an important role in human physiology: it functions in over 600 enzymes as a cofactor, is crucial for nerve conduction and cardiac contractility, enhances resistance of DNA and RNA against oxidative stress by stabilizing their tertiary structure, cell cycle control and cell proliferation depend on Mg^{2+}, and ATP has to bind Mg^{2+} to be biologically active(2). Nevertheless, general practitioners frequently do

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Conflicts of interest

No conflict of interest.

not evaluate serum Mg^{2+}(3, 4). Hypermagnesemia occurs usually in preeclamptic women after Mg^{2+} therapy and in patients with end-stage renal disease (ESRD). Elevated Mg^{2+} concentrations cause muscle weakness, fatigue and somnolence. Hypomagnesemia is more common and occurs in up to 15% of the general population(5). Mild to moderate hypomagnesemia frequently does not cause symptoms, if more significant muscle spasms, arrhythmia, and seizures occur. Increasing evidence points to chronic hypomagnesemia as a risk factor for developing hypertension, type 2 diabetes mellitus, metabolic syndrome, chronic kidney disease, and cancer(6–16).

Blood Mg^{2+} concentration reflects the equilibrium between intestinal Mg^{2+} reabsorption and renal Mg^{2+} excretion. In the small intestine Mg^{2+} undergoes reabsorption in a paracellular fashion, in between epithelial cells (17, 18) (Fig. 1). This allows for reabsorption of large amounts of Mg^{2+} as this mode of reabsorption is non-saturable(18) (Fig. 1A). Mg^{2+} reabsorption in the cecum and colon occurs in a transcellular fashion via apical Mg^{2+} channels TRPM6 and TRPM7 which in contrast to paracellular transport is saturable (Fig. 1A, B). Intestinal Mg^{2+} reabsorption is poorly regulated and depends on Mg^{2+} intake.

The kidneys are the primary regulators of Mg^{2+} homeostasis. About 80% of the serum Mg^{2+} is filtered in the glomerulus and about 95–99% of the filtered Mg^{2+} is recovered along the nephron(2) (Fig. 1C). The main location for renal Mg^{2+} reabsorption with 65–75% is the thick ascending limb of Henle (TAL). Here Mg^{2+} transport occurs in a paracellular mode(20) (Fig. 1C). In the TAL the major driving force for Mg^{2+} reabsorption is the lumen-positive transepithelial potential difference. The fine-tuning of renal Mg^{2+} reabsorption occurs in the distal convoluted tubule (DCT) via apical TRPM6 and TRPM7 channels(21) (Fig. 1D). Here, the negative membrane potential is a prerequisite for Mg^{2+} reabsorption(22, 23). As in the gut it is unclear how Mg^{2+} is exported on the basolateral side. Hypomagnesemias are due to medication side effects (Table 1), insufficient dietary Mg^{2+} intake, or rare inherited renal defects, which are divided in hypercalciuric, Gitelman-like, and other hypomagnesemias (Table 2).

Hypercalciuric hypomagnesemias

These disorders share that the gene defect impairs paracellular Mg^{2+} and Ca^{2+} reabsorption in the TAL by disrupting the lumen-positive transepithelial potential difference and thereby cause hypercalciuria and hypomagnesemia.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC)

Symptoms in FHHNC include hypomagnesemia, and hypocalcemia due to urinary Ca^{2+} and Mg^{2+} losses, nephrocalcinosis and in some patients eye involvement(42–44). Infrequent symptoms are dRTA, hypocitraturia, nephrolithiasis, hyperuricemia, recurrent UTIs, polyuria and failure to thrive(45, 46). Neurological symptoms due to hypomagnesemia are rare. While patients grow relatively well tooth enamel defects can occur(47, 48). In the teens to twenties patients can develop chronic kidney disease and may require renal replacement therapy(45). Recessive mutations in *Claudin-16* (*CLDN16*) were published(49). A genotype-phenotype correlation for *CLDN16* mutations was published with earlier onset of ESRD with two loss of function mutations(45). Patients with FHHNC and ocular involvement were

found to have mutations in a related gene called Claudin-19 (*CLDN19*)(50). Both proteins are strongly expressed in renal tissue, specifically in the TAL(49–51). Claudin-19 is also found in ocular tissue(50). Claudin-16 and 19 both co-localize to tight junctions (TJ) in the TAL and the DCT(49, 50). TJ are protein complexes in between epithelial cells which determine the permeability of the epithelial barrier(51). Both proteins interact with each other and form heterodimers(52, 53). Initially, it was thought that *CLDN16* mutations would impair tubular Ca^{2+} and Mg^{2+} reabsorption by disturbing a Ca^{2+} and Mg^{2+} selective channel(49). However, the mechanism contributing to hypomagnesemia and hypercalciuria turned out to be more complex (Fig. 2A). The lumen-positive potential difference, which is the major driving force for paracellular Ca^{2+} and Mg^{2+} reabsorption, is created by two different mechanisms: Secretion of K^+ via ROMK, which is driven by the reabsorption of Na^+, K^+ and Cl^- via NKCC2 in the TAL, contributes to the lumen-positive potential. The second component of the lumen-positive potential is called the dilution potential and is explained in detail in Fig. 2A. Mutations in *CLDN16* and *19* affect the creation of the dilution potential and result in a less lumen-positive potential(52).

It remains unclear why FHHNC patients develop ESRD. Japanese cattle lacking CLDN16 developed tubulointerstitial nephritis with hypocalcemia but no hypomagnesemia(54, 55). Immature tubular epithelial cells with loss of polarization and renal tubular dysplasia raise concern for a developmental defect. *Cldn16* knockout mice displayed hypercalciuria and hypomagnesemia but no renal impairment(56). *Cldn19* knockout mice show disorganized tight junctions in Schwann cells, abnormal behavior and neuropathy but no ocular or renal phenotype(57). At this point it is thought that hypercalciuria and nephrocalcinosis contribute to the development of ESRD. Hydrochlorothiazide treatment reduces hypercalciuria but had no effect on slowing down ESRD progression(58).

Autosomal dominant hypocalcemia (ADH)

ADH is characterized by hypocalcemia, hypercalciuria, kidney stones, normal to inappropriately low PTH levels, and about 50% of all ADH patients have hypomagnesemia resulting in seizures and carpopedal spasms(59, 60). ADH is caused by gain-of-function mutations in the calcium sensing receptor (CaSR)(61). In the TAL the CaSR is expressed at the basolateral membrane(62) (Fig. 2B). *CASR* mutations result in a higher sensitivity of the CaSR contributing to a higher receptor response despite physiological extracellular Ca^{2+} concentrations, mimicking hypercalcemia(59). Subsequently, PTH is suppressed and renal Ca^{2+} and Mg^{2+} absorption is impaired(62, 63). Patients with severe gain-of-function mutations in CaSR can develop Bartter syndrome (BS) (BS type V)(64). Here, gain-of function *CASR* mutations result in impaired NKCC2 and ROMK function. Different mechanisms of how CaSR activation contributes to urinary Na^+, K^+ and Cl^- losses are discussed (Fig. 2B)(62, 65, 66). All these possibilities decrease the lumen-positive potential.

Recent studies outlined a novel, intricate mechanism how CaSR activation results in renal Ca^{2+} and Mg^{2+} wasting involving the calcineurin signaling pathway, NFAT, specific miRNAs, and Claudin-14 (Fig. 2B)(67, 68). CASR stimulation enhances Claudin 14 expression, a negative regulator of Claudins-16 and 19. This diminishes the lumen-positive

potential and contributes to urinary Ca^{2+} and Mg^{2+} losses. Downregulation of Claudin-14 and upregulation of Claudin-16 was confirmed in a *Casr*$^{-/-}$ mouse model(69).

Classical Bartter syndrome (cBS)

The features of cBS (or BS type III) are polyuria, renal salt wasting, concentration defect, hypokalemic metabolic alkalosis, and hypercalciuria(70). Later in life patients can develop a Gitelman-like phenotype with hypocalciuria and hypomagnesemia(71, 72). Classical BS is caused by recessive mutations in the *CLCNKB* gene which encodes the basolateral chloride channel CLC-Kb (Fig. 2C)(73, 74). Another form of antenatal BS (BS with deafness, or BS type IV) is due to recessive mutations in the *BSND* gene. *BSND* encodes the protein Barttin which is a subunit of the CLC-Kb channel (Fig. 2C)(75). This form of BS can also result in hypomagnesemia but may initially not display hypercalciuria and is therefore typically included in the Gitelman-like forms of hypomagnesemia (Table 2)(76). Mutations in *CLCNKB* and *BSND* disturb the intracellular Cl^- regulation. This affects apical NCC and NKCC2 function which subsequently interferes with the generation of the lumen-positive potential and may so disturb tubular Mg^{2+} absorption(77, 78).

Gitelman-like hypomagnesemias

Mg^{2+} reabsorption in the DCT depends critically on the negative membrane potential. In this group mutated proteins are involved in Na^+, K^+, or Cl^- transport in the DCT, thereby disturbing the negative membrane potential. All disorders in this group result in hypocalciuria, volume contraction, hypotension, and activation of the renin-angiotensin system (RAS), which then drives K^+ and H^+ secretion, thus contributing to hypokalemia and metabolic alkalosis (Table 2).

Gitelman syndrome (GS)

GS is one of the most common tubulopathies with a prevalence of 1:40,000(79). GS is characterized by hypokalemic alkalosis, hypocalciuria and hypomagnesemia(80). Symptoms include muscle weakness, fatigue, salt craving, thirst, nocturia, and carpopedal spasms. Clinical presentation is heterogenous ranging from asymptomatic to severe impairment of quality of life(81). Recessive mutations were published in the *SLC12A3* gene which encodes the Na-Cl cotransporter NCC(82). In up to 40% of patients the second mutation cannot be detected possibly due to deep intronic location or large genomic rearrangements(83–85). A *Ncc* knockout mouse model confirmed the human GS phenotype with hypomagnesemia and hypocalciuria but lacked volume contraction and metabolic alkalosis(86, 87). *Ncc* mutant mice displayed hypotension, volume contraction, metabolic alkalosis, and urinary Mg^{2+} wasting(88). Hypocalciuria and hypomagnesemia in GS are thought to be the result of compensatory paracellular volume, Na^+ and Ca^{2+} reabsorption in the PT due to volume contraction(28, 87). Regarding hypomagnesemia different hypotheses were proposed including K^+ depletion, dysfunctional Mg^{2+} absorption, atrophy of the DCT and renal Mg^{2+} wasting. *Ncc*$^{-/-}$ mice and thiazide treatment in wild-type (WT) mice displayed urinary Mg^{2+} wasting due to less apical Trpm6 expression(28). GS patients require lifelong Mg^{2+} and possibly K^+ supplementation, as well as spironolactone, amiloride or eplerenone.

EAST syndrome

EAST is an abbreviation for epilepsy, ataxia, sensorineural deafness, and salt loosing tubulopathy(89). These patients present in early infancy with seizures, speech and motor delay, hearing impairments, and cerebellar symptoms such as ataxia, tremor, and dysdiadochokinesia(90). Hypokalemic metabolic alkalosis, hypocalciuria and hypomagnesemia develop during the disease course(91). Recessive mutations in the basolateral, inwardly rectifying K^+ channel Kir4.1 were identified(89, 92). Consistent with the disease phenotype Kir4.1 expression was found in the brain, stria vascularis of the inner ear and DCT. *Kir4.1*$^{-/-}$ mice displayed a phenotype similar to humans(89). Kir4.1 forms heteromeric complexes with another K^+ channel called Kir5.1(93). The basolateral Kir4.1/5.1 complex works together with the basolateral Na^+/K^+-ATPase by recycling K^+ ions that entered the cell in exchange for extruding Na^+ ions (Fig. 3A)(92, 94). The distribution of extracellular and intracellular K^+ is crucial for the generation of the negative membrane potential. The neurological phenotype is due to depolarization of neurons thus lowering the threshold for seizures(92).

Isolated dominant hypomagnesemia (IDH)

IDH is characterized by hypocalciuria and hypomagnesemia but lacks hypokalemic metabolic alkalosis, salt wasting or RAS stimulation. Patients present with seizures in childhood, severe hypomagnesemia, developmental delay due to repeated seizures, urinary Mg^{2+} wasting but normal or even upregulated intestinal Mg^{2+} absorption. Dominant mutations in two different genes, *FXYD2* and *KCNA1*, cause IDH(95, 96). *FXYD2* encodes the γ subunit of the Na^+/K^+-ATPase (Fig. 3B). FXYD2 enhances ATP and decreases Na^+ affinity in a tissue-specific manner(97, 98). Only one mutation (glycine to arginine at position 41) has been identified which has a dominant-negative effect resulting in incorrect trafficking and perinuclear accumulation of the mutant protein(95, 99). Lack of *FXYD2* in humans or mice does not cause Mg^{2+} abnormalities. The mechanism how *FXYD2* mutations cause Mg^{2+} dysregulation remains unclear.

A second gene contributing to IDH was identified with the *KCNA1* gene which encodes the apical voltage-gated channel Kv1.1(96). Patients display muscle cramps, tetany, tremors and muscle weakness. Urinary Mg^{2+} wasting but no abnormalities regarding Ca^{2+} were found. Ataxia and myokymia, an involuntary form of localized muscle trembling, were found in all affected patients. Interestingly, *KNCA1* mutations were previously described in other patients with ataxia and myokymia(100). However, only the N255D (asparagine to aspartic acid at position 255) mutation caused hypomagnesemia(96). Kv1.1 co-localizes with TRPM6 in the DCT but does not regulate TRPM6. The Kv1.1 channel forms tetramers and co-expression of mutant and WT KV1.1 results in a dominant-negative effect of the mutant Kv1.1. As channel trafficking is preserved probably gating of the channel pore is affected resulting in diminished negative membrane potential (Fig. 3B).

HNF1B nephropathy

Mutations in *HNF1B* result in a spectrum of symptoms including maturity-onset diabetes of the young type 5 (MODY5), hyperechogenic kidneys, multicystic and glomerulocystic kidney disease, renal hypoplasia, renal agenesis, hyperuricemic nephropathy, renal cysts and

diabetes syndrome(101–105). About 50% of HNF1B patients have hypomagnesemia due to renal Mg^{2+} losses and display hypocalciuria(106). Mutations in *HNF1B* can be inherited in an autosomal dominant fashion or occur *de novo*. *HNF1B* encodes the transcription factor hepatocyte nuclear factor 1β, a member of the homeodomain-containing superfamily, which is crucial for renal and pancreatic development. HNF1B regulates other proteins which are involved in renal Mg^{2+} absorption such as FXYD2(106). Several HNF1B binding sites were identified in the *FXYD2* promoter and *HNF1B* mutations impair *FXYD2* transcription(107).

Transient neonatal hyperphenylalaninemia and primapterinuria

Transient neonatal hyperphenylalaninemia and primapterinuria is a benign neonatal syndrome without long-term sequela(108). However, three adults with hypomagnesemia, renal Mg^{2+} losses, and MODY were found to have recessive mutations in the gene *PCBD1* which usually causes the transient metabolic disease(109). The encoded protein Pterin-4α carbinolamine dehydratase forms a heterotetrameric complex by physically interacting with HNF1B and is a crucial dimerization factor(109). Defective dimerization due to mutant *PCBD1* results in proteolytic instability of the PCBD1-HNF1B complex and subsequently impaired HNF1B-mediated stimulation of *FXYD2* promoter activity (Fig. 3C).

Other hypomagnesemia

This group includes different inherited diseases which may not fit in one of the above listed groups (Table 2).

Isolated recessive hypomagnesemia (IRH)

IRH is caused by recessive mutations in the *EGF* gene(38). The affected individuals developed seizures in infancy, developmental delay, hypomagnesemia due to renal Mg^{2+} wasting, but no other electrolyte abnormality(110). A homozygous mutation in the *pro-EGF* gene, encoding for the epidermal growth factor, was identified(38). Pro-EGF is a type 1 transmembrane protein with 1207 amino acids (aa) which is cleaved to the final EGF (53 aa length). The identified mutation is located in the cytosolic C-terminus within a sorting motif and results in impaired EGF secretion(38). WT EGF is secreted and binds to EGF receptor at the basolateral membrane of the DCT, thereby activating a tyrosine kinase which stimulates TRPM6(38) (Fig. 4). The significance of EGF as an autocrine magnesiotropic hormone was confirmed by the chimeric human/mouse anti-EGF antibody cetuximab in chemotherapy as patients treated with cetuximab develop hypomagnesemia(111).

Hypomagnesemia with secondary hypocalcemia (HSH)

Patients with this rare condition present with generalized seizures in early infancy, severely low serum Mg^{2+} (approximately 0.2 mmol/L), and hypocalcemia(112). Perfusion studies in humans indicated an intestinal and renal Mg^{2+} leak(113). The cause of hypocalcemia is poorly understood but it seems that low Mg^{2+} impairs PTH secretion(114). Consistent with this finding HSH patients have inappropriately low PTH concentrations. The hypocalcemia does not respond to Ca^{2+} or vitamin D supplements but only to Mg^{2+} supplementation(115). Recessive mutations in the gene encoding the transient receptor potential melastatin 6 channel (TRPM6), a member of the TRP family with a C-terminal kinase domain, were

published(116, 117). TRPM6 is expressed in the gut (e.g. duodenum, jejunum, colon) and the kidney (e.g. DCT)(118). TRPM6 is homologous to TRPM7, another channel permeable to Ca^{2+} and Mg^{2+}. Both, TRPM6 and 7 form heteromers, interact and modify each other(119). TRPM6 is regulated my multiple factors including hypomagnesemia, estradiol, and calcineurin inhibitors(35, 120, 121).

Hypomagnesemia with impaired brain development

Patients present with seizures, hypomagnesemia (~0.4–0.5 mmol/L), muscle weakness, vertigo and headaches. Heterozygous and homozygous *CNNM2* mutations were found in affected individuals but some mutation carriers remained asymptomatic(122). *CNNM2* encodes the transmembrane protein Cyclin M2, which is expressed at the basolateral side of the TAL and DCT. Truncating and missense mutations were published, the latter impaired Mg^{2+} sensitive current(122, 123). The physiological function of CNNM2 remains unknown, but involves possibly a role as Mg^{2+} transporter or Mg^{2+} sensor(122, 124).

Mitochondrial Hypomagnesemia

Metabolic disease with hypercholesterolemia, and hypertension was found linked with hypomagnesemia in a large kindred(125). Interestingly, only females were affected pointing to mitochondrial inheritance. Hypomagnesemia was associated with hypocalciuria indicating involvement of the DCT. A mutation in the mitochondrially encoded isoleucine tRNA gene was found. The mutation affects a thymidine residue adjacent to the anticodon triplet, which is extremely conserved and critical for codon-anticodon recognition. Interestingly, additional mitochondrial disorders have been identified causing hypomagnesemia also involving the TAL(126–128). Both TAL and DCT have high energy requirements but the exact mechanism how mitochondrial disorders contribute to hypomagnesemia remains unclear.

Conclusion

Despite the identification of several genes with rare Mendelian disorders our understanding of renal Mg^{2+} homeostasis remains very incomplete. Most of the inherited conditions alter the lumen-positive potential in the TAL or the negative membrane potential in the DCT and only few conditions affect directly a Mg^{2+} channel. As most of the patients present with neurological symptoms practitioners need to be vigilant and neurologists should be educated about the nature of these conditions.

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List of abbreviations

ADH	autosomal dominant hypocalcemia

BS	Bartter syndrome
BSND	Barttin
Ca^{2+}	calcium
CaSR	calcium sensing receptor
Cl^{-}	chloride
CLDN	claudin
DCT	distal convoluted tubule
EAST	epilepsy, ataxia, sensorineural deafness and tubulopathy
EGF	epidermal growth factor
ESRD	end-stage renal disease
FHHNC	familial hypomagnesemia with hypercalciuria and nephrocalciosis
GS	Gitelman syndrome
HSH	hypomagnesemia with secondary hypocalcemia
IDH	isolated dominant hypomagnesemia
IRH	isolated recessive hypomagnesemia
K^{+}	potassium
Kir4.1	inwardly rectifying potassium channel 4.1
Kv1.1	voltage-gated potassium channel 1.1
Mg^{2+}	magnesium
NCC	Na-Cl cotransporter
NKCC2	Na-K-Cl cotransporter
NFAT	nuclear factor of activated T-cells
PT	proximal tubule
RAS	renin-angiotensin system
ROMK	renal outer medullary potassium channel
TAL	thick ascending limb of Henle
TRPM6	transient receptor potential melastatin 6 channel

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Key Bullet Points

- Mild to moderate chronic hypomagnesemia is a common problem in up to 15% of the general population but symptoms are usually absent or mild.
- Because hypomagnesemia is associated with multiple common human disorders (e.g. hypertension, type 2 diabetes mellitus, metabolic syndrome, chronic kidney disease, and cancer) this electrolyte deserves better monitoring.
- Hypomagnesemia can be caused by insufficient dietary Mg^{2+} intake, medication side effects, and rare inherited disorders resulting in urinary Mg^{2+} wasting.
- Inherited forms of hypomagnesemia are divided into hypercalciuric (mostly affecting the TAL), Gitelman-like (mostly affecting the DCT), and other forms of hypomagnesemia (mostly affecting the DCT).
- Most forms of inherited hypomagnesemia do not affect directly a Mg^{2+} channel but rather affect Mg^{2+} reabsorption by altering the lumen-positive potential difference in the TAL or the negative membrane potential in the DCT.

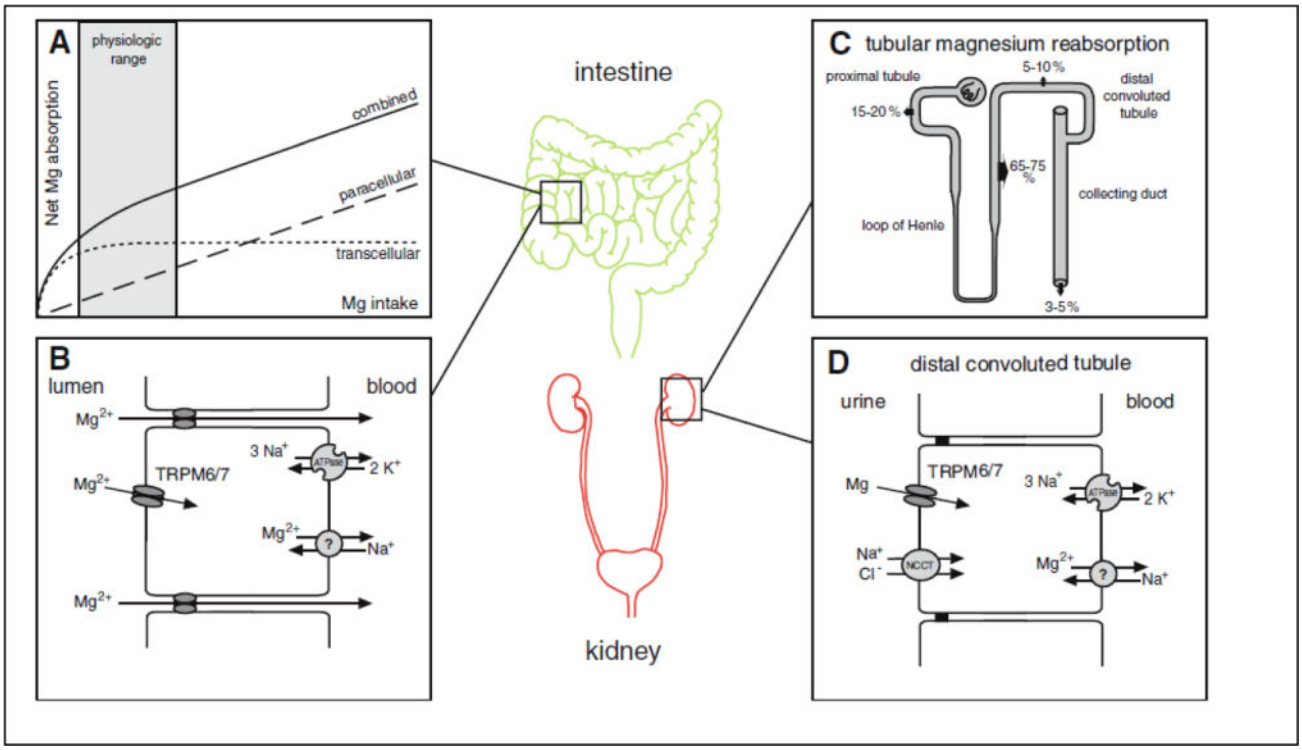

Fig. 1. Intestinal and renal mechanisms of Mg^{2+} reabsorption

Intestinal Mg^{2+} reabsorption occurs predominantly in the small intestine, cecum and colon(17, 18) (Fig. 1). Intestinal Mg^{2+} reabsorption varies between 25–80% with higher Mg^{2+} reabsorption in low Mg^{2+} states(17, 18). **A**) Intestinal Mg^{2+} reabsorption occurs in a paracellular, non-saturable fashion, while Mg^{2+} reabsorption in the cecum and colon occurs in a transcellular, saturable fashion. **B**) Transcellular Mg^{2+} transport in the intestinal tract occurs via apical Mg^{2+} channels TRPM6 and TRPM7. It is thought that a Mg^{2+} ATPase and/or a Mg^{2+}-Na^{+} exchanger facilitates basolateral Mg^{2+} extrusion(18). **C**) About 2.4 g of Mg^{2+} is filtered by the glomerulus daily. As 95 to 99% of the filtered Mg^{2+} is reabsorbed along the nephron only approximately 100 mg of Mg^{2+} is excreted per day. In contrast to many other electrolytes the proximal tubule reabsorbs only 10–25% of Mg^{2+} and the majority of Mg^{2+} is reabsorbed in the TAL. **D**) Similar to the intestinal tract, TRPM6 and TRPM7 channels in the apical membrane mediate transcellular Mg^{2+} reabsorption in the DCT. Reprinted with permission from(19).

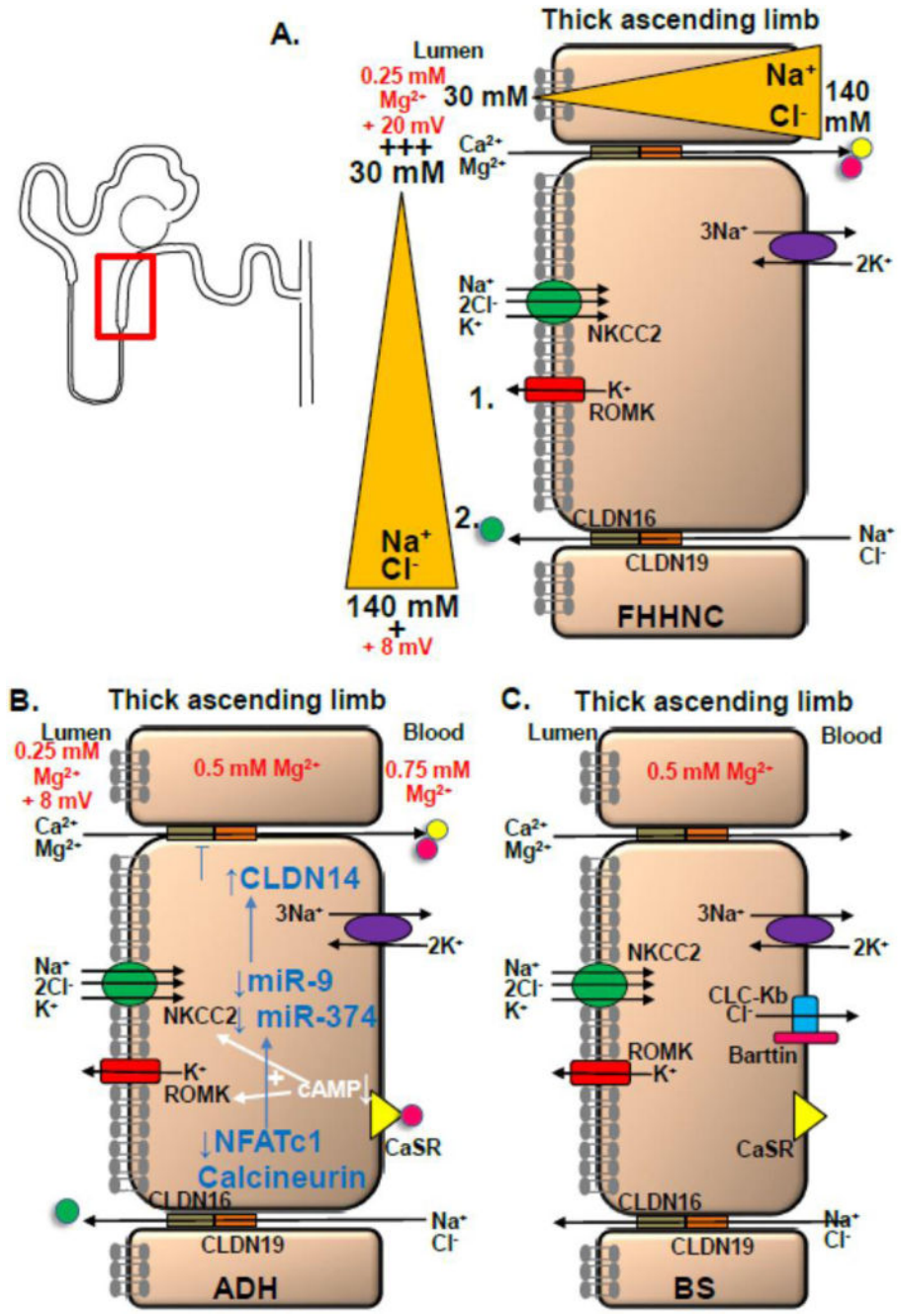

Fig. 2. Mechanisms of hypercalciuric hypomagnesemias

Hypercalcuric hypomagnesemias such as FHHNC, ADH, and BS affect the TAL by disturbing the lumen-positive potential. **A**) Potassium secretion via ROMK constitutes one component of the lumen-positive potential (1.). The second (2.) component is due to the dilution potential: At the beginning of the TAL luminal Na^+ has a concentration of 140 mM which decreases to 30 mM along the downstream TAL. As more Na^+ and Cl^- is absorbed along the TAL a major Na^+ and Cl^- gradient between lumen and interstitium is created. A higher Na^+ and Cl^- concentration in the interstitium result in a driving force for both ions to leak back into the tubular lumen. This is where Claudin-16 and 19 come into play. While

Claudin-16 increases the Na^+ permeability, Claudin-19 decreases the Cl^- permeability, thereby contributing to a high permeability ratio of Na^+ to Cl^- and providing a strong cation selectivity for Na^+ causing the lumen-positive potential to rise from 8 to 20 mV or even higher. **B**) Different mechanisms contribute to hypomagnesemia in case of CaSR activation including an inhibitable adenylcyclase and activation of inhibitory G proteins resulting in decreased intracellular cAMP levels (cAMP usually enhances NKCC2 and ROMK activities). A novel pathway involves calcineurin signaling and downregulation of NFAT which reduces transcription of two miRNAs called miR9 and miR374 (blue arrows). With CaSR activation there is downregulation of miR9 and 374 and upregulation of Claudin-14 which suppresses the Claudin-16 and 19 complex, thereby interfering with the lumen-positive lumen potential. **C**) Mutations in *CLCNKB* and *BSND* disturb the intracellular Cl^- regulation which is thought to affect apical NCC and NKCC2 function. Impaired NCC and NKCC2 function interferes with the generation of the lumen-positive potential and may thereby disturb tubular Mg^{2+} absorption.

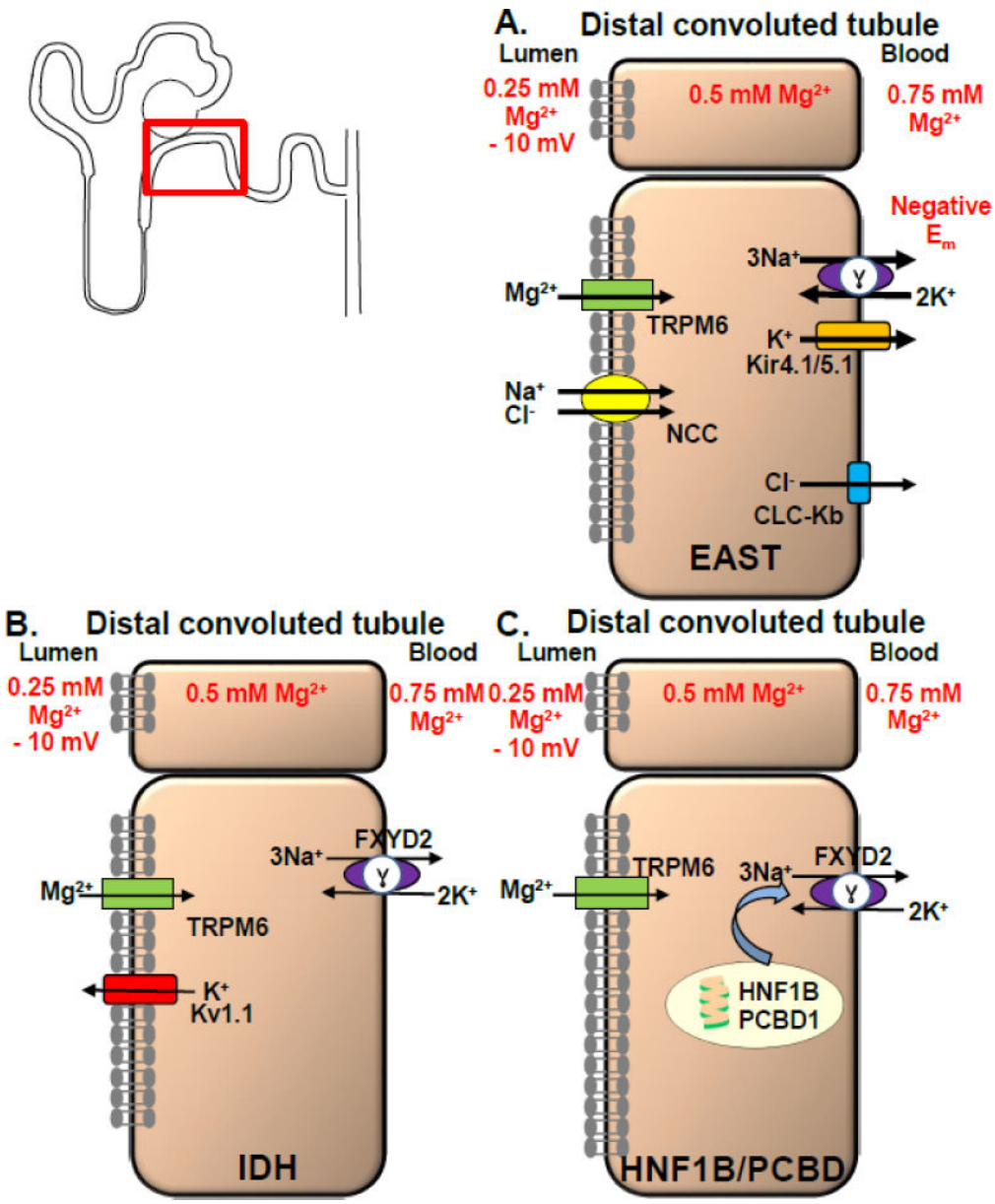

Fig. 3. Mechanisms of Gitelman-like hypomagnesemias

Gitelman-like hypomagnesemias such as EAST, IDH, and HNF1B/PCBD affect the DCT by disturbing the negative membrane potential. **A**) EAST syndrome: The negative membrane potential promotes basolateral chloride exit via CLC-Kb and apical Mg^{2+} entrance via TRPM6 due to a favorable electrical gradient. In case of *Kir4.1* mutations Na^+/K^+-ATPase function is decreased and due to loss of K^+ recycling via Kir4.1/5.1 a less negative membrane potential is the result. This reduces the basolateral chloride export and inhibits apical reabsorption of Na^+ and Cl^- via NCC and Mg^{2+} via TRPM6(66, 92). Urinary salt wasting activates RAS, enhances Na^+ reabsorption via ENaC and K^+ and H^+ secretion in the collecting duct which explains the hypokalemic metabolic alkalosis. **B**) The mechanism how *FXYD2* mutations in IDH cause Mg^{2+} dysregulation remains unclear. Different hypotheses consider that a dysfunctional γ subunit of the Na^+/K^+-ATPase may result in reduced

intracellular K^+ concentration (which may depolarize the apical membrane and so impair Mg^{2+} reabsorption), altered intracellular Na^+ concentration (which could affect a putative basolateral Mg^{2+}-Na^+ exchanger), the γ subunit could also be important for the Mg^{2+}-Na^+ exchanger, and a defective Na^+/K^+-ATPase disturbs potentially cellular energy metabolism and may result in a higher risk of apoptosis. For IDH due to *KCNA1* mutations: The negative membrane voltage, which is maintained by an apical K^+ efflux via Kv1.1, is crucial as Mg^{2+} uptake from the ultrafiltrate via the TRPM6 channel is driven by a favorable negative membrane voltage. **C**) HNF1B and PCBD1 form a heteromeric complex and stimulate FXYD2 transcription, which encodes a subunit of the Na^+/K^+-ATPase.

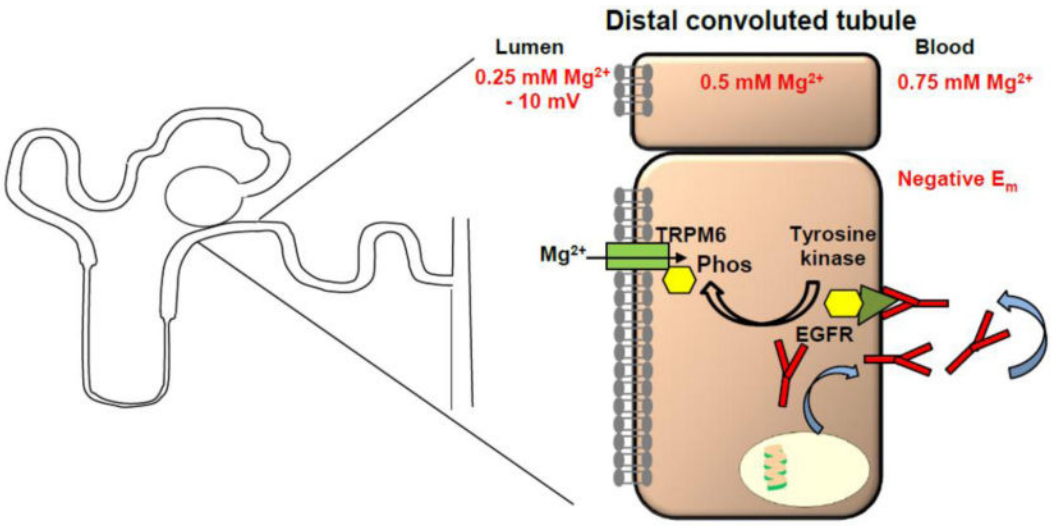

Fig. 4. Mechanisms of other hypomagnesemias

Other hypomagnesemias such as IRH and HSH affect the DCT by impairing EGF secretion or dysfunctional TRPM6 channels. In IRH EGF is less secreted at the basolateral side and therefore there is less autocrine stimulation of the basolateral EGF receptor (EGFR). EGFR stimulates apical TRPM6 channel via phosphorylation by a tyrosine kinase.

Table 1

Medications contributing to hypomagnesemia.

Medications contributing to hypomagnesemia	**Mechanism**
Proton pump inhibitors (e.g. omeprazole)	Decreased intestinal Mg^{2+} reabsorption via TRPM6(18, 24, 25) Tubulo-interstitial nephritis(26)
Diuretics (e.g. furosemide, thiazide)	↓ lumen positive potential difference in TAL blocking Na^{+} reabsorption in DCT affects membrane potential(27, 28)
Platinum derivatives (e.g. cisplatin, carboplatin)	Necrotic nephropathy(29) PT and DCT injury(30–33)
Calcineurin inhibitors (e.g. cyclosporine A, tacrolimus)	Downregulation of Claudin-16 downregulation of TRPM6(34–37)
Epidermal growth factor receptor inhibitor (e.g. cetuximab)	Blockade of EGF receptor and lack of TRPM6 stimulation(38, 39)
Antimicrobials (e.g. aminoglycosides, amphotericin B, pentamidine,…)	PT damage, Fanconi syndrome(40, 41)

Table 2

List of inherited forms of hypomagnesemia.

Disorder	Inheritance	Gene locus	Gene (Protein)	Function
Hypercalciuric hypomagnesemias				
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis	AR	3q28	*CLDN16* (Claudin-16)	tight junction protein
Familial hypomagnesemia with hypercalciuria and nephrocalcinosis plus ocular involvement	AR	1p34	*CLDN19* (Claudin-19)	tight junction protein
Classical Bartter syndrome (type 3)	AR	1p36	*ClC-Kb* (ClC subunit B)	basolateral Chloride channel
Autosomal dominant hypocalcemia/Bartter syndrome (type 5)	AD	3q13	*CASR* (CaSR)	Calcium sensing receptor
Gitelman-like hypomagnesemias				
Gitelman syndrome	AR	16q13	*SLC12A3* (NCC)	Na^+-Cl^- cotransporter
Antenatal Bartter syndrome with sensorineural deafness (type 4)	AR	1p31	*BSND* (Barttin)	Subunit of ClC-Ka/b
EAST/SeSAME syndrome	AR	1q23	*KCNJ10* (Kir4.1)	apical potassium channel
Isolated dominant hypomagnesemia	AD	11q23	*FXYD2* (FXYD2)	Na^+/K^+-ATPase (γ subunit)
	AD	12p13	*KCNA1* (Kv1.1)	apical potassium channel
HNF1B nephropathy	AD	17q12	*HNF1B* (HNF1beta)	transcription factor
Hypomagnesemia after transient neonatal hyperphenylalaninemia	AR	10q22	*PCBD1* (PCBD1)	tetrahydrobiopterin metabolism
Other hypomagnesemias				
Isolated recessive hypomagnesemia	AR	4q25	*EGF* (Pro-EGF)	epidermal growth factor
Hypomagnesemia with secondary hypocalcemia	AR	9q22	*TRPM6* (TRPM6)	apical Mg^{2+} channel
Hypomagnesemia with impaired brain development	AD/AR	10q24	*CNNM2* (CNNM2)	Cyclin M2
Hypomagnesemia with metabolic syndrome	maternal	mtDNA	*MTTI* (MTTI)	mitochondrial tRNA for isoleucine
Hyperuricemia, pulmonary hypertension and progressive renal failure (HUPRA)	AR	19q13	*SARS2* (SARS2)	seryl-tRNA synthetase