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Invited Review

Insights into the molecular nature of magnesium homeostasis

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Konrad, Martin, Karl P. Schlingmann, and Thomas Gudermann. Insights into the molecular nature of magnesium homeostasis. *Am J Physiol Renal Physiol* 286: F599–F605, 2004; 10.1152/ajprenal.00312.2003.—Magnesium is an important cofactor for many biological processes, such as protein synthesis, nucleic acid stability, or neuromuscular excitability. Extracellular magnesium concentration is tightly regulated by the extent of intestinal absorption and renal excretion. Despite the critical role of magnesium handling, the exact mechanisms mediating transepithelial transport remained obscure. In the past few years, the genetic disclosure of inborn errors of magnesium handling revealed several new proteins along with already known molecules unexpectedly involved in renal epithelial magnesium transport, e.g., paracellin-1, a key player in paracellular magnesium and calcium reabsorption in the thick ascending limb or the γ-subunit of the Na^+-K^+-ATPase in the distal convoluted tubule. In this review, we focus on TRPM6, an ion channel of the "transient receptor potential" (TRP) gene family, which, when mutated, causes a combined defect of intestinal magnesium absorption and renal magnesium conservation as observed in primary hypomagnesemia with secondary hypocalcemia.

hypomagnesemia; secondary hypocalcemia; long transient receptor potential; genetics

MAGNESIUM PHYSIOLOGY

MAGNESIUM IS PREDOMINANTLY stored in bone and the intracellular compartments of muscle and soft tissues; <1% of total body magnesium is circulating in the blood (11). In normal subjects, serum magnesium levels are kept in a narrow range (0.7–1.1 mmol/l). Magnesium homeostasis depends on the balance between intestinal absorption and renal excretion. Within physiological ranges, diminished magnesium intake is balanced by enhanced magnesium absorption in the intestine and reduced renal excretion. These transport processes are regulated by metabolic and hormonal influences (25, 51).

The principal site of magnesium absorption is the small intestine, with smaller amounts being absorbed in the colon. Intestinal magnesium absorption occurs via two different pathways: a saturable active transcellular transport and a nonsaturable paracellular passive transport (12, 25) (Fig. 1*A*). Saturation kinetics of the transcellular transport system are explained by the limited transport capacity of active transport. At low intraluminal concentrations, magnesium is absorbed primarily via the active transcellular route and, with rising concentrations, via the paracellular pathway, yielding a curvilinear function for total absorption (Fig. 1*B*).

In the kidney, ~80% of total serum magnesium is filtered in the glomeruli with >95% being reabsorbed along the nephron. Magnesium reabsorption differs in quantity and kinetics depending on the different nephron segments; 15–20% is reabsorbed in the proximal tubule of the adult kidney. Interestingly, the immature kidney of the newborn can absorb up to 70% of the filtered magnesium in this nephron segment (9). From early childhood on, the majority of magnesium (~70%) is reabsorbed in the loop of Henle, especially in the cortical thick ascending limb (TAL). Transport in this segment is passive and paracellular, driven by the lumen-positive transepithelial voltage (Fig. 2*A*). Although only 5–10% of the filtered magnesium is reabsorbed in the distal convoluted tubule (DCT), the part of the nephron where the fine adjustment of renal excretion is accomplished. As there is no significant reabsorption of magnesium in the collecting duct, the reabsorption rate in the DCT defines the final urinary magnesium excretion. Magnesium transport in this part of the nephron is active and transcellular in nature (Fig. 2*B*). Physiological studies indicate that apical entry into DCT cells is mediated by a specific and regulated magnesium channel driven by a favorable transmembrane voltage (8). The mechanism of basolateral transport into the interstitium is unknown. Magnesium has to be extruded against an unfavorable electrochemical gradient. Most physiological studies favor a sodium-dependent exchange mechanism (50). Magnesium entry into DCT cells appears to be the rate-limiting step and the site of regulation. Finally, 3–5% of the filtered magnesium is excreted in the urine. Magnesium transport in the distal tubule has been recently reviewed in detail by Dai et al. (8).

The evidence for the magnesium transport pathways described above mainly evolved from physiological studies. During recent years, the analysis of disease phenotypes characterized by disturbances in magnesium handling turned out to be very helpful for a better understanding of magnesium homeostasis (Table 1; for a review, see Refs. 6 and 26).

The first example was the identification of mutations in *CLDN16* encoding paracellin-1 by a positional cloning approach in familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) by Simon et al. in 1999 (60). As paracellin-1 is almost exclusively expressed in the TAL, these findings nicely confirmed the hypothesis of Rodriguez-Soriano

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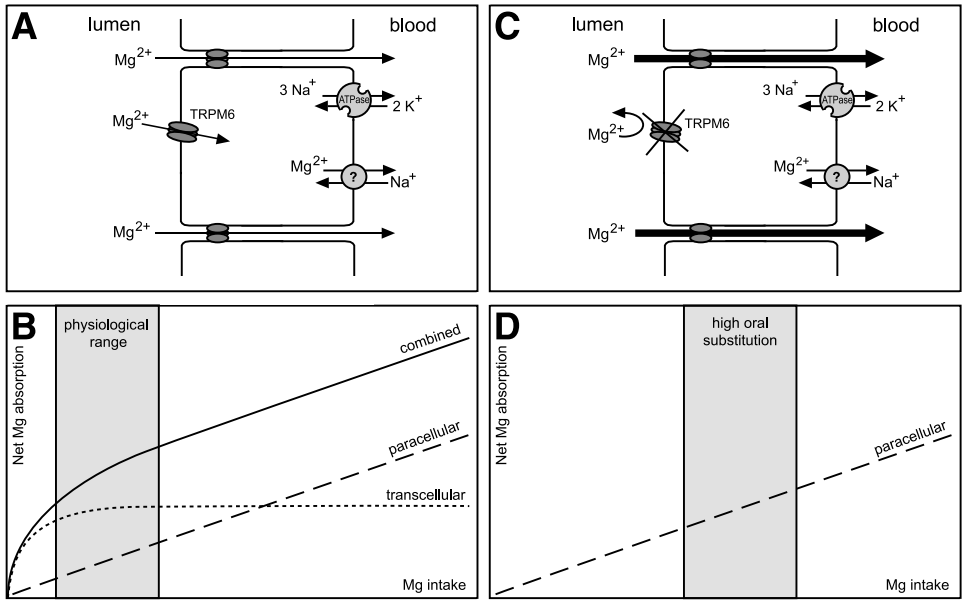

Fig. 1. *A*: proposed model of intestinal magnesium absorption. *B*: intestinal magnesium absorption vs. intake. The curvilinear function (solid line) results from a nonsaturable paracellular and a saturable transcellular transport. *C*: in hypomagnesemia with secondary hypocalcemia, all magnesium is absorbed via the paracellur pathway because TRPM6 mutations lead to a disruption of the transcellular route. *D*: in hypomagnesemia with secondary hypocalcemia, high oral magnesium substitution allows a more effective use of the paracellular magnesium absorption mechanism.

and Vallo (52), who predicted defective magnesium and calcium reabsorption in this nephron segment as the primary defect in FHHNC. Paracellin-1 could be characterized as a member of the claudin family involved in tight junction formation. From the disease phenotype, it was concluded that paracellin-1 might regulate the paracellular transport of magnesium and calcium ions by contributing to a selective paracellular conductance by building a pore permitting paracellular fluxes of magnesium and calcium down their electrochemical gradients (60, 72). This hypothesis is supported by the recent observation that two other claudins (*CLDN4* and *CLDN14*) indeed influence ion selectivity by creating charge-selective channels through the tight-junction barrier (7, 63).

An unexpected finding was the identification of a trafficking mutation in the γ-subunit of the Na^+-K^+-ATPase as the cause of isolated dominant hypomagnesemia (IDH) (34). Coexpression with the mutant γ-subunit abolished the correct routing of the entire Na^+-K^+-ATPase complex to the plasma membrane (34). However, another group observed an isolated trafficking defect of the mutant γ-subunit (with normal membrane insertion of α- and β-subunits) (49). Their results indicated that a failure of the mutant γ-subunit to modulate the kinetics of the Na^+-K^+-ATPase may lead to a decrease in pump activity and to a secondary reduction in transcellular magnesium reabsorption. However, the precise cellular mechanism of decreased magnesium reabsorption remains to be determined as well as the concomitant finding of hypocalciuria in IDH.

Mutations in the Ca^{2+}/Mg^{2+}-sensing receptor (*CASR*), either activating or inactivating mutations, are also frequently associated with disturbed magnesium handling. Activating *CASR* mutations lead to autosomal-dominant hypoparathyroidism (ADH) (48), which is characterized by hypocalcemia and hypercalciuria but also frequently cause hypomagnesemia in affected individuals (44). This is explained by a shift of the set point of the receptor to a level of enhanced sensitivity not only for extracellular Ca^{2+} but also for Mg^{2+}. This results in decreased parathyroid hormone (PTH) secretion and inhibition of the reabsorption of divalent cations in the cortical TAL and DCT (4).

In contrast, patients with heterozygous inactivating *CASR* mutations exhibit hypocalciuric hypercalcemia, described as familial hypocalciuric hypercalcemia (FHH) (47), but affected individuals also show a tendency toward hypermagnesemia (31). Homozygous or compound heterozygous inactivation of

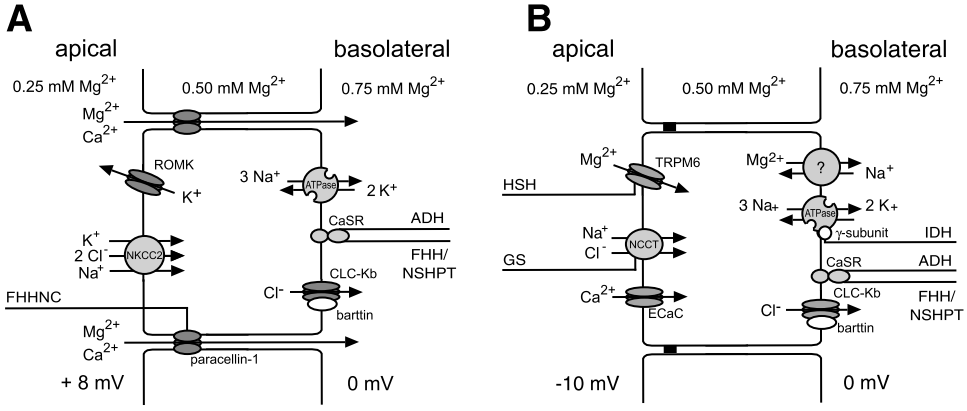

Fig. 2. *A*: magnesium reabsorption in the thick ascending limb of the loop of Henle. Driving force for the reabsorption against a concentration gradient is a lumen-positive voltage gradient generated by the reabsorption of NaCl. FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; ADH, autosomal-dominant hypoparathyroidism; FHH/NSHPT, familial hypomagnesemia/neonatal severe hyperparathyroidism. *B*: magnesium reabsorption in the distal convoluted tubule. Active transcellular transport mediated by an apical entry through a magnesium channel and a basolateral exit, presumably via a Na^+/Mg^{2+} exchange mechanism. HSH, hypomagnesemia with secondary hypocalcemia; GS, Gitelman variant of Bartter syndrome; IDH, isolated dominant hypomagnesemia.

Table 1. *Inherited disorders of magnesium handling*

Disorder	Inheritance	Locus	Gene	Protein
Familial hypomagnesemia with hypercalciuria/ nephrocalcinosis	AR	3q28	*CLDN16*	Paracellin-1 (tight junction protein)
Isolated dominant hypomagnesemia with hypocalciuria	AD	11q23	*FXYD2*	γ-Subunit of the Na^+-K^+-ATPase
	AD	?	?	?
Isolated recessive hypomagnesemia with normocalciuria	AR	?	?	?
Autosomal-dominant hypoparathyroidism	AD	3q21	*CASR*	CaSR (Ca^{2+}/Mg^{2+}-sensing receptor)
Familial hypocalciuric hypercalcemia	AD	3q21	*CASR*	CaSR (Ca^{2+}/Mg^{2+}-sensing receptor)
Neonatal severe hyperparathyroidism	AR	3q21	*CASR*	CaSR (Ca^{2+}/Mg^{2+}-sensing receptor)
Gitelman variant of Bartter syndrome	AR	16q13	*SLC12A3*	NCCT (Na^+-Cl^--cotransporter)
Hypomagnesemia with secondary hypocalcemia	AR	9q22	*TRPM6*	TRPM6 (putative ion channel)

AR, autosomal-recessive; AD, autosomal-dominant.

the *CASR* results in neonatal severe hyperparathyroidism (NSHPT), characterized by marked elevation in serum calcium and PTH levels from birth (47). This disease is generally lethal unless total a parathyroidectomy is performed early in life. Besides hypercalcemia, some NSHPT patients also have overt hypermagnesemia (31).

The most frequent hereditary tubular disorder affecting renal magnesium handling is the Gitelman variant of Bartter syndrome (GS). This primary salt-wasting disorder is caused by mutations in the sodium-chloride cotransporter (NCCT) of the DCT (61). Clinical features of GS, in addition to persistent hypokalemia and metabolic alkalosis, include the combination of hypomagnesemia and hypocalciuria (3), a finding pathognomonic for disturbed DCT function. A conclusive explanation for the hypomagnesemia regularly observed in these patients is still lacking. An increased rate of apoptosis, as shown in rats after chronic thiazide administration (30), might reduce the absorptive surface area of the DCT, and thereby compromise magnesium absorption in GS.

Recently, mutations in two members of the atypical WNK kinase family, namely, WNK1 and WNK4, have been identified in patients with pseudohypoaldosteronism type II, an inherited form of hypertension and hyperkalemia (71). The observation that a disturbance in WNK kinase activity leads to an increase in NCCT-mediated NaCl reabsorption in the DCT (75) is in accordance with the phenotype of patients with pseudohypoaldosteronism type II, which is largely opposite to that of Gitelman patients. However, in contrast to overt hypercalciuria, a tendency toward hypermagnesemia was not observed in these patients (1, 33).

The most recent example of a genetic approach yielding a new molecule involved in epithelial magnesium transport is the characterization of TRPM6 mutations in primary hypomagnesemia with secondary hypocalcemia, which allowed the identification of the first component of intestinal magnesium absorption (56, 68).

HYPOMAGNESEMIA WITH SECONDARY HYPOCALCEMIA

Hypomagnesemia with secondary hypocalcemia (HSH) is an autosomal-recessive disorder that manifests in early infancy with generalized convulsions or other symptoms of increased neuromuscular excitability like muscle spasms or tetany. It was first described by Paunier et al. in 1968 (43). Failure of early diagnosis or noncompliance with treatment can be fatal or result in permanent neurological damage.

Laboratory evaluation reveals extremely low serum magnesium and low serum calcium levels. The mechanism leading to hypocalcemia is still not completely understood. Several factors seem to contribute to an impairment of PTH action. In severe hypomagnesemia, a failure of the parathyroid gland has been reported by Anast and colleagues (2), resulting from impaired synthesis and/or release of PTH. Consistently, PTH levels in HSH patients (at initial presentation) were found to be inappropriately low. Furthermore, several findings pointed to a role of end-organ resistance to PTH for the development of hypocalcemia, as studies have shown the inability of administered PTH to correct the hypocalcemia in continuing hypomagnesemia (35). In addition, PTH-induced release of calcium from bone is substantially impaired in hypomagnesemia (53), as magnesium depletion interferes with the generation of cAMP in response to PTH (14). The hypocalcemia observed in HSH is resistant to treatment with calcium or vitamin D. Relief of clinical symptoms, normocalcemia, and normalization of PTH levels can only be achieved by administration of high doses of magnesium (58).

Transport studies in HSH patients pointed to a primary defect in intestinal magnesium absorption (36). However, in some patients an additional renal leak for magnesium was suspected (32).

A gene locus (HOMG1) for HSH had been mapped to Chr 9q22 in 1997 (69) and further refined to a critical interval of ~1 cM (67). Recently, two independent groups identified *TRPM6* in this critical interval and reported presumable loss-of-function mutations, mainly truncating mutations, as the underlying cause of HSH (Fig. 3) (56, 68). *TRPM6* codes for a new member of the transient receptor potential (TRP) family of cation channels (Fig. 4). TRPM6 protein shows highest homology to TRPM7, which was characterized as a calcium- and magnesium-permeable ion channel regulated by Mg-ATP (40). By RT-PCR and in situ hybridization, TRPM6 expression could be demonstrated along the entire small intestine and colon but also in distal tubule cells in the kidney. Immunofluorescence studies with an antibody generated against murine TRPM6 could localize TRPM6 to the apical membrane of the DCT (65). The detection of TRPM6 expression in the DCT confirms the theory of Cole and Quamme (6) of an additional role of renal magnesium wasting in the pathogenesis of HSH. This was also supported by intravenous magnesium-loading tests in HSH patients, which disclosed a considerable renal magnesium leak, albeit they were still hypomagnesemic (68).

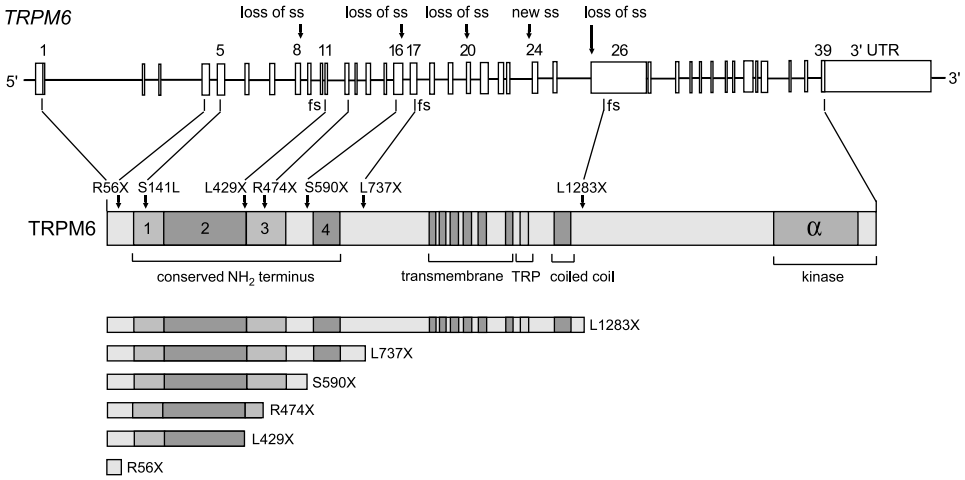

Fig. 3. Schematic model of TRPM6. Genomic organization (*top*) and mRNA structure of TRPM6 (*middle*). Functional domains are deduced from the TRPm7 model described by Nadler et al. (40). All mutations reported are indicated (48, 58). Note the high proportion of splice site (ss) or truncating mutations (*bottom*); only 1 point mutation has been detected so far. fs, Frameshift; TRP, transient receptor potential; UTR, untranslated region.

The observation that in HSH patients the substitution of high oral doses of magnesium achieves at least subnormal serum magnesium levels supports the theory of two independent intestinal transport systems for magnesium. TRPM6 probably represents a molecular component of active transcellular magnesium transport. An increased intraluminal magnesium concentration (by increased oral intake) enables compensation for the defect in active transcellular transport by increasing absorption via the passive paracellular pathway (Fig. 1, *C* and *D*).

TRP CATION CHANNELS

The TRP protein superfamily comprises >20 related cation channels playing important roles in a wide variety of physiological processes, for example, phototransduction, sensory physiology, and regulation of smooth muscle tone (39). *Drosophila* carrying the *trp* mutation are inflicted with impaired vision because of the lack of a specific Ca^{2+} influx pathway in the photoreceptors (18). The identification of the *trp* gene product as a cation channel and the rewarding search for TRP homologs in other species paved the way for the discovery of a whole new family of cation channels whose physiological importance we are just beginning to appreciate.

Based on structural homology and on systematic glycosylation scanning analysis (64), TRP proteins are allocated to the structural superfamily of six-transmembrane ion channels encompassing most voltage-gated K^+ channels, the cyclic nucleotide-gated channel family, and single-transmembrane cassettes of voltage-activated Ca^{2+} and Na^+ channels. Both NH_2 and COOH termini of TRP proteins are thought to be located intracellularly, and a putative pore-forming region is bordered by transmembrane *domains 5* and *6*. Analogous to the situation

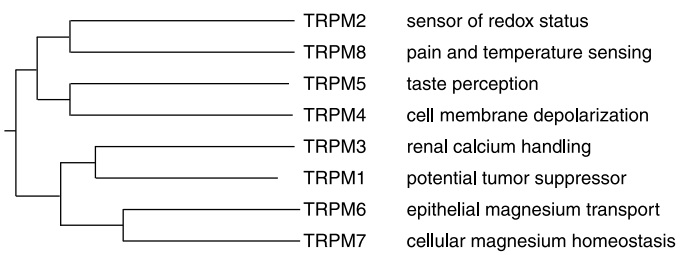

Fig. 4. Dendrogram and proposed physiological role of the TRPM ion channels.

with the other aforementioned hexahelical cation channels, four TRP protein subunits assemble to form a functional channel complex. The principles governing the assembly of tetrameric complexes have recently been defined for heterologously expressed TRPC proteins (22) and were independently worked out for rat brain synaptosomes (15).

The conventional TRP proteins can be allocated to three subfamilies: TRPC, TRPV, and TRPM. Three additional, more distantly related subfamilies, i.e., TRPML, TRPN, and TRPP, have recently been defined (38) but are not dealt with further in the present review. Within the NH_2 termini of several TRP channels, ankyrin-binding motifs can be discerned: 3–6 in TRPC and TRPV proteins and up to 29 in TRPNs. Immediately downstream of the sixth transmembrane domain, TRPC and TRPM proteins contain a conserved stretch of a 25-amino acid-spanning TRP domain that commences with the invariable EWKFAR sequence, the so-called TRP box.

TRPC proteins all share a common gating mechanism that involves the activation of phospholipase C isoforms. For nearly all TRPC members, Ca^{2+} store-dependent and -independent activation mechanisms have been proposed (5, 23, 38). However, the physiological role of distinct TRPC proteins still remains largely obscure. The genetic inactivation of TRPC2 in mice unveiled its cardinal role as a sensory transduction channel for the pheromone response (29, 62), whereas disruption of the TRPC4 gene resulted in impaired endothelium-dependent vasorelaxation in mutant mice (13). TRPC6 has been shown to represent a receptor-operated, diacylglycerol-stimulative fairly nonselective cation channel (23) involved in the regulation of vascular smooth muscle tone (24) and of intravascular pressure-induced depolarization and contraction of resistance arteries (70).

TRPV family members are involved in sensory processes and in the absorption of Ca^{2+} in intestine and kidney. Four of the six current TRPV proteins, TRPV1–4, are temperature-activated (summarized in Ref. 66). In addition, TRPV1 is also activated by ligands such as vanilloid compounds like capsaicin, an active ingredient in hot chili peppers, the endogenous cannabinoid ligand anandamide, as well as by 12-lipoxygenase metabolites of arachidonic acid (59). TRPV4 is gated by numerous physical and chemical stimuli including cell swelling, heat, phorbol esters, and probably also by endogenous arachidonic acid-derived ligands (42).

TRPV5 and TRPV6 have been initially cloned from vitamin D-responsive Ca^{2+}-transporting epithelia and termed epithelial calcium channels ECaC1 and ECaC2 (19, 45). Functional expression revealed the characteristic features of a constitutively activated Ca^{2+} permeability, a large $Ca^{2+} > Na^{+}$ selectivity, and a current-voltage relationship showing inward rectification (20). Localization to the apical membrane of epithelial cells of the small intestine as well as in the distal tubule, predominantly in the DCT, together with functional properties predispose these TRPV channels to a major role in the intestinal uptake and renal reabsorption of Ca^{2+} (10), as shown by expression studies. However, TRPV6 has also been shown to exhibit salient features of CRAC channels when expressed in vitro (39, 76).

Currently, the TRPM proteins are considerably less understood compared with their TRPC and TRPV relatives. TRPM proteins display the structural hallmark of exceptionally long intracellular NH_2 and COOH termini. The founding member, TRPM1 (melastatin), was detected as a potential tumor suppressor in malignant melanoma cells, probably mediating Ca^{2+} entry on heterologous expression (73). Two different variants of TRPM3 have also been shown to represent Ca^{2+}-permeable ion channels (28), the shorter variant being activated by cell swelling (16). Due to its prominent expression in the kidney, a role of TRPM3 in renal Ca^{2+} handling has been proposed. TRPM4 and TRPM5 highlight a novel facet of the functional properties of TRPM proteins in that both proteins give rise to Ca^{2+}-activated cation channels permeable to monovalent cations and mediating cell membrane depolarization (21, 27, 41). Interestingly, both TRPM4 and TRPM5 display voltage-dependent modulation and rapid activation and deactivation kinetics on receptor stimulation and depolarization. TRPM5 is enriched in taste receptor cells and provides for the receptor potential underlying sweet, amino acid, and bitter taste perception (39, 77). A different role in sensory physiology has been ascribed to TRPM8, which is expressed in sensory neurons and prostate carcinoma cells and activated by menthol, icillin, and cool temperatures (summarized in Ref. 39).

Three members of the TRPM family, i.e., TRPM2, TRPM6, and TRPM7, are set apart from other known ion channels because they harbor enzyme domains in their respective COOH termini and thus represent prototypes of an intriguing new protein family of enzyme-coupled ion channels. TRPM2 is COOH terminally fused to an ADP-pyrophosphatase and has found to be activated by one of the products of NAD hydrolysis, ADP-ribose (46). Subsequently, TRPM2 gating by NAD was also reported (55) and received considerable attention because an increased NAD production resulting from an altered cellular redox state might explain TRPM2 sensitivity toward H_2O_2 and other agents eliciting reactive oxygen and nitrogen species (17). As TRPM2 activation may result in a massive deleterious Ca^{2+} influx, the latter ion channel epitomizes a new molecular link between the metabolic and redox state of the cell and Ca^{2+} entry and apoptosis.

TRPM6 as well as TRPM7 contain protein kinase domains in their COOH termini, which bear sequence similarity to elongation factor 2 (eEF-2) serine/threonine kinases and other proteins, which contain an α-kinase domain (54). Despite the lack of detectable sequence homology to classical eukaryotic protein kinases, the crystal structure of TRPM7 kinase surprisingly revealed a striking structural similarity to the catalytic core of eukaryotic protein kinases as well as to metabolic enzymes with ATP-grasp domains (74).

TRPM7 is widely expressed, and targeted disruption of the channel gene in cell lines proved to be lethal, underpinning a salient and nonredundant role in cell physiology (40). Interestingly, TRPM7 exhibits significant Mg^{2+} permeation, a rather unusual feature of other cation channels, and is inhibited by cytosolic Mg^{2+} as well as Mg-ATP. A systematic analysis of the permeation properties of TRPM7 revealed that the latter channel has the unique property of conducting a wide range of divalent trace metal ions, some of which have detrimental consequences for the cell on intoxication (37). In light of its broad expression pattern and its constitutive activity, TRPM7 may provide a general mechanism for the entry of divalent cations into cells. However, recent data suggest that TRPM7 represents a primarily magnesium-permeable ion channel required for the cellular uptake of magnesium (57). The magnesium permeability seems to be modulated by a functional coupling between TRPM7's ion channel and kinase domains indicated by coordinated changes in phosphotransferase activity and ion flow. By the phosphorylation of yet unidentified target proteins, the kinase domain might thus be involved in a negative-feedback mechanism that inhibits a further uptake of magnesium in the presence of rising intracellular magnesium concentrations (57).

TRPM6 is closely related to TRPM7 and represents the second TRP protein being fused to a COOH-terminal α-kinase domain. The TRPM6 gene is composed of 39 exons coding for a total of 2,022 amino acid residues. TRPM6 mRNA shows a more restricted expression pattern, with the highest levels along the intestine (duodenum, jejunum, ileum, colon) and the DCT of the kidney (56). Immunohistochemistry showes a complete colocalization with the Na^{+}-Cl^{-} cotransporter NCCT (also serving as a DCT marker) but also with parvalbumin and calbindin-D_{28K}, two cytosolic proteins that putatively act as intracellular (calcium and) magnesium buffers (65).

The functional expression of TRPM6 in HEK cells revealed large outwardly rectifying whole cell currents strongly resembling the currents observed for TRPM7 with a reversal potential near 0 mV (65). Permeation characteristics, with currents almost exclusively carried by divalent cations with a higher affinity for Mg^{2+} than Ca^{2+}, support the role of TRPM6 as the apical Mg^{2+} influx pathway. Furthermore, TRPM6, analogous to TRPM7, exhibits a marked sensitivity to intracellular Mg^{2+}. Thus one might speculate about an inhibition of TRPM6-mediated Mg^{2+} uptake by rising intracellular Mg^{2+} concentrations as a possible mechanism of a regulated intestinal and renal Mg^{2+} (re)absorption. This inhibition might be mediated in part by intracellular Mg-ATP as shown for TRPM7 by Nadler and colleagues (40), who suggested a possible link to cellular energy metabolism.

In contrast to wild-type TRPM6, transfection of two TRPM6 mutants found in HSH patients yielded no detectable currents compared with nontransfected controls (65). However, both mutants analyzed lead to an early truncation of the TRPM6 protein lacking the pore-forming transmembrane domains. Certainly, the analysis of point mutations will be more helpful in elucidating functional aspects of the TRPM6 ion channel disturbed in HSH. In conclusion, the genetic analysis of HSH patients together with the expression studies and the functional

channel characteristics highlight a crucial role of TRPM6 for epithelial Mg^{2+} transport in intestine and kidney. However, considering the tetrameric structure of TRP channels, a participation of other members of the TRP family in the formation of the physiologically active apical Mg^{2+} channel in intestine and kidney cannot be excluded.

In summary, careful clinical observation in combination with molecular genetic analysis considerably enlarged the current understanding of epithelial magnesium transport. It might be expected that the characterization of other disease phenotypes associated with disturbed magnesium handling will lead to the identification of additional proteins involved in magnesium homeostasis. Hopefully, this knowledge will provide starting points for the development of new therapeutic strategies in these rare diseases.

GRANTS

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