Transient receptor potential melastatin 6 and 7 channels, magnesium transport, and vascular biology: implications in hypertension

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Touyz RM. Transient receptor potential melastatin 6 and 7 channels, magnesium transport, and vascular biology: implications in hypertension. Am J Physiol Heart Circ Physiol 294: H1103–H1118, 2008. First published January 11, 2008; doi:10.1152/ajpheart.00903.2007.—Magnesium, an essential intracellular cation, is critically involved in many biochemical reactions involved in the regulation of vascular tone and integrity. Decreased magnesium concentration has been implicated in altered vascular reactivity, endothelial dysfunction, vascular inflammation, and structural remodeling, processes important in vascular changes and target organ damage associated with hypertension. Until recently, very little was known about mechanisms regulating cellular magnesium homeostasis, and processes controlling transmembrane magnesium transport had been demonstrated only at the functional level. Two cation channels of the transient receptor potential melastatin (TRPM) cation channel family have now been identified as magnesium transporters, TRPM6 and TRPM7. These unique proteins, termed chanzymes because they possess a channel and a kinase domain, are differentially expressed, with TRPM6 being found primarily in epithelial cells and TRPM7 occurring ubiquitously. Vascular TRPM7 is modulated by vasoactive agents, pressure, stretch, and osmotic changes and may be a novel mechanotransducer. In addition to its magnesium transporter function, TRPM7 has been implicated as a signaling kinase involved in vascular smooth muscle cell growth, apoptosis, adhesion, contraction, cytoskeletal organization, and migration, important processes involved in vascular remodeling associated with hypertension and other vascular diseases. Emerging evidence suggests that vascular TRPM7 function may be altered in hypertension. This review discusses the importance of magnesium in vascular biology and implications in hypertension and highlights the transport systems, particularly TRPM6 and TRPM7, which may play a role in the control of vascular magnesium homeostasis. Since the recent identification and characterization of Mg2+-selective transporters, there has been enormous interest in the field. However, there is still a paucity of information, and much research is needed to clarify the exact mechanisms of magnesium regulation in the cardiovascular system and the implications of aberrant transmembrane magnesium transport in the pathogenesis of hypertension and other vascular diseases.

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Hypertension is a major risk factor influencing the global burden of morbidity and mortality (10). High blood pressure is associated with functional changes and structural remodeling of the vasculature, heart, and kidneys, which lead to cardiovascular disease, stroke, and renal failure (125, 188–190). The most common form of hypertension is “essential hypertension,” the cause of which remains unknown. Many factors have been implicated in the pathogenesis of essential hypertension, including the renin-angiotensin-aldosterone system, salt, sympathetic nervous system hyperactivation, and alterations in cellular cations, such as Ca2+, Na+, K+, and Mg2+ (13, 166–172, 188–190).

Epidemiological data indicate an inverse association between dietary magnesium consumption and blood pressure: the higher the magnesium intake, the lower the blood pressure (49, 64, 90, 231, 245, 246, 253). Experimental and clinical studies suggest that Mg2+ deficiency plays a role in the pathogenesis of hypertension (100–106, 117–124, 217–230). Exact mechanisms for this are unclear, but effects on the vasculature have been implicated. Magnesium is a vasodilator, and when it is infused intravenously in patients, blood pressure decreases significantly (114). Magnesium influences vascular smooth muscle cell (VSMC) growth, inflammation, and membrane permeability to Na+ and Ca2+, which also may be important in the development of hypertension (177, 257–259). An impairment in ionic metabolism, specifically an increase in intracellular Ca2+ levels and a decrease in intracellular Mg2+ concentrations, was proposed by Resnick more than 10 years ago (166–172).

Magnesium is the second most common intracellular cation and the most abundant intracellular divalent cation (6, 7, 69,
It is stored primarily in bone and the intracellular compartments of muscle and soft tissues, with \(<1\%\) of total body magnesium circulating in the blood (177). Normal serum magnesium levels are maintained in a narrow range (0.7–1.1 mmol/l) (177). Extracellular magnesium concentration is tightly regulated by intestinal absorption and renal excretion. These transport systems are regulated by metabolic and hormonal factors.

At the cellular level, \(\text{Mg}^{2+}\) is involved in many essential physiological and biochemical processes regulating cardiovascular function, including contraction and dilation, growth and inflammation, production of vasoactive agents, and protein and nucleic acid synthesis (24, 135). Magnesium is critical for myriad enzymatic reactions, particularly those involving kinases, and it also regulates ion channels (177). Mammalian cells tightly control magnesium levels by specific regulatory mechanisms operating at the level of intracellular compartmentalization and intracellular magnesium buffering and at the level of magnesium entry and efflux across the cell membrane. Within cells, magnesium compartmentalizes primarily in nuclei, mitochondria, and endo/sarcoplasmic reticulum, with concentrations of total magnesium within these organelles being \(\sim 116\) mmol/kg cell dry weight (44). Intracellular free levels of magnesium (\([\text{Mg}^{2+}]_i\)) are relatively stable at \(\sim 0.6\) mmol/l (28, 175, 176, 210). Important in the regulation of \([\text{Mg}^{2+}]_i\) is cellular buffering of the cation (232) with ATP being the main cellular magnesium buffering system (62).

The tight regulation of \([\text{Mg}^{2+}]_i\) also involves magnesium influx and efflux across the cell membrane. Although magnesium is such an abundant cytosolic cation and is so important in biological processes, little is known about the transport mechanisms regulating magnesium homeostasis. This was recently highlighted in an editorial comment entitled “The Mysteries of Magnesium Transport” (145). Transporters and exchangers that have been implicated in transmembrane \(\text{Mg}^{2+}\) transport include the \(\text{Na}^+/\text{Mg}^{2+}\) exchanger, \(\text{Mg}^{2+}/\text{Ca}^{2+}\) exchanger, and recently identified cation channels, including transient receptor potential melastatin 6 and 7 channels (TRPM6 and TRPM7) (141, 175, 176, 195–198). The present review discusses the importance of magnesium in vascular biology in hypertension and focuses on transport systems, particularly TRPM6 and TRPM7, in the control of cellular magnesium homeostasis.

**Magnesium and Vascular Biology**

Magnesium influences vascular tone by regulating endothelial function and VSMC function (116, 117, 119, 132, 212, 215). Magnesium stimulates prostacyclin production and nitric oxide (NO) formation and promotes endothelium-dependent and endothelium-independent vasodilation (67, 154, 158). Isolated vessels exposed to reduced levels of magnesium display a transient vasorelaxation followed by sustained constriction. In the presence of endothelial damage, low magnesium induces a sustained contraction without the transient vasorelaxation phase (67, 154), suggesting that magnesium could have a dual effect in the regulation of vascular reactivity, depending on the integrity of the endothelium. An intact endothelium prevents against the unfavorable effects of hypomagnesemia, whereas in the presence of endothelial damage, as is the case in many cardiovascular diseases, the compensatory vasodilatory effect is absent and low magnesium promotes constriction (40, 158, 203, 215).

Magnesium also modulates vascular tone and reactivity by altering responses to vasoconstrictor and vasodilator agents. Increased extracellular magnesium concentration blunts vasoconstrictor actions and potentiates vasorelaxant properties of vasoactive agents (107, 136, 199, 201–203). These effects may be related to altered binding of agonists to their specific cell membrane receptors and/or to production of vasoactive agents such as endothelin-1 (ET-1), angiotensin II (ANG II), and prostacyclin (PGI2) (120, 186, 243). In magnesium-deficient rats, plasma ET-1 levels are elevated, whereas in magnesium-supplemented rats, plasma ET-1 levels are reduced (116, 117, 119, 120). Increased magnesium attenuates ET-1-induced contraction, and reduced magnesium levels augment ET-1-stimulated contraction (116, 117, 119, 120). Magnesium stimulates endothelial release of vasodilator PGI2 from human umbilical arteries and cultured umbilical vein endothelial cells (24). These effects may be particularly relevant in MgSO4 treatment of eclampsia and preeclampsia (36, 100, 102, 130, 184, 201).

Another possible mechanism whereby magnesium could have some bearing on vascular function is via its antioxidant, anti-inflammatory, and growth regulatory properties (224, 229, 240–242). Vascular cells are a rich source of reactive oxygen species, which directly alter VSMC contraction and growth (189, 214, 229). Magnesium has antioxidant/anti-inflammatory properties that could attenuate damaging actions of oxidative stress and inflammation in the vasculature (135, 240–242), thereby preventing vascular injury. These effects may be important in hypertension, where generation of reactive oxygen species is increased and \([\text{Mg}^{2+}]_i\) is reduced (214, 228).

**Magnesium and Hypertension**

Magnesium influences blood pressure, in part, by regulating vascular tone and reactivity (87, 116–120). The direct vascular effect of magnesium was first suggested in the early 1900s, when it was observed in clinical studies that magnesium salt infusion lowered blood pressure acutely via a reduction in peripheral vascular resistance (23). Experimental and clinical studies have demonstrated that magnesium administration induces vasodilation, improves blood flow, decreases vascular resistance, increases capacitance function of peripheral, coronary, renal, and cerebral arteries, attenuates agonist-induced vasoconstriction, and reduces blood pressure (17–20, 128, 205). Decreased magnesium levels have opposite effects causing contraction, potentiation of agonist-evoked vasoconstriction, and increased vascular tone and blood pressure.

**Magnesium and experimental hypertension.** Hypomagnesemia and decreased tissue content of magnesium have been reported in various experimental models of hypertension (4, 9, 86, 91, 131, 218). \([\text{Mg}^{2+}]_i\) is lower in isolated cardiomyocytes and VSMCs and in circulating cells from spontaneously hypertensive rats (SHR) and deoxycorticosterone acetate (DOCA) salt hypertensive rats compared with normotensive controls (4, 9, 86, 148, 183, 234). In experimental models with severe hypertension, such as stroke-prone SHR and DOCA-treated SHR, \([\text{Mg}^{2+}]_i\) is negatively and \([\text{Ca}^{2+}]_i\) is positively correlated with systolic blood pressure, whereas \([\text{Mg}^{2+}]_i\) and \([\text{Ca}^{2+}]_i\) are inversely associated (4, 91), suggesting that \([\text{Mg}^{2+}]_i\) may be involved in blood pressure regulation by competing with cal-

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Magnesium and human hypertension. Epidemiological studies have linked hypertension and cardiac disease with “soft water,” low in magnesium, and protection against cardiovascular disease with “hard water,” high in magnesium (231, 245, 246, 253). The relationship between dietary magnesium intake and blood pressure in humans was first demonstrated in the Honolulu Heart study (90) and later by many epidemiological and clinical investigations that supported the hypothesis that increased magnesium intake contributes to prevention of hypertension and cardiovascular disease (12, 15, 85, 95, 97, 231, 245). Clinical studies have shown, for the most part, some form of hypomagnesemia (serum and/or tissue) in hypertensive patients, with significant inverse correlations between magnesium concentration and blood pressure (163, 217, 219, 220, 246, 247) (Table 1). A relationship also has been described among the renin-angiotensin system, magnesium, and blood pressure. High-renin hypertensive patients tend to have significantly lower serum magnesium levels than normotensive subjects (166), and serum magnesium is inversely associated with plasma renin activity (PRA) (38, 166). Since increased PRA indicates activation of the renin-angiotensin system, it may be possible that ANG II-dependent hypertension is associated, at least in part, with vascular and cardiac effects of hypomagnesemia. A negative dependency between [Mg$^{2+}$], and arterial compliance in humans has been shown: the lower the [Mg$^{2+}$], the stiffer the blood vessels and the greater the blood pressure (172). Moreover, hypertensive patients with low magnesium levels were found to require a greater number of antihypertensive medications compared with normomagnesemic patients (245).

In further support of an association between hypertension and magnesium, Wilson et al. (248) described a genetic form of hypertension associated with hypercholesterolemia and hypomagnesemia. The phenotype is transmitted on the maternal lineage with a pattern indicating mitochondrial inheritance. Analysis of the mitochondrial genome of the maternal lineage identified a mutation in a mitochondrial tRNA. Inborn errors of magnesium handling may contribute to the magnesium wasting in these patients.

Not all clinical studies have reported magnesium depletion in hypertension. Some studies found no differences in serum magnesium levels or in [Mg$^{2+}$], in hypertensive patients (26, 54, 60, 252), whereas others reported increased erythrocyte and platelet [Mg$^{2+}$], in patients with essential hypertension (54, 80, 185) (Table 1). Furthermore, a few epidemiological studies failed to show an association between magnesium intake and blood pressure or cardiovascular disease (22, 245). It is evident that not all hypertensive patients are hypomagnesemic, and not all patients with magnesium deficiency are hypertensive.

Despite these inconsistencies, there are subgroups of hypertensive patients who consistently demonstrate altered magnesium metabolism. These include individuals of African descent, obese subjects, patients with severe or malignant forms of hypertension, elderly patients, and those with metabolic syndrome (14–16, 59, 64, 70, 71, 93, 94, 129, 204). Such hypertensive patients may be magnesium sensitive and potentially could benefit from magnesium supplementation.

Underlying mechanisms for altered magnesium homeostasis in hypertension are unclear, but inborn errors of magnesium handling, decreased membrane permeability, altered Na$^+$/Mg$^{2+}$ exchange, defective membrane binding, and impaired cellular responsiveness have been implicated (66). My group recently suggested that dysregulation of vascular TRPM6 and/or TRPM7 also may play a role in aberrant cellular magnesium handling in hypertension (78, 206, 230).

| Table 1. Serum and intracellular magnesium status in patients with hypertension |
|-----------------|-----------------|-----------------|-----------------|
| Parameter       | Patient Profile | Reference       |
| Serum Mg$^{2+}$ | EH-diabetic     | 14, 178, 209, 219, 220 |
|                 | HT-sensitive    | 15, 16, 244, 256 |
|                 | Preeclampsia    | 100, 102, 173    |
|                 | Obese-HT       | 38,39           |
| Erythrocyte Mg$^{2+}$ | EH       | 58, 61, 178, 187, 219, 220 |
|                 | Malignant HT    | 220             |
|                 | EH-obese       | 38,39           |
|                 | HT-cyclosporine | 5               |
| Lymphocyte/leukocyte Mg$^{2+}$ | EH | 42             |
|                 | HT-cyclosporine | 5               |
| Platelet Mg$^{2+}$ | EH       | 101             |
|                 | EH-diabetes    | 9, 219, 220     |
|                 | Malignant HT    | 39              |
|                 | EH-obese       | 38,39           |
|                 | Salt-sensitive HT | 249         |

EH, essential hypertension; HT, hypertension; HT-cyclosporine, renal transplant patients with hypertension and treated with cyclosporine; ↓, decrease; ↑, increase; —, no change.
Molecular Regulation of Cellular Magnesium

The total cellular magnesium content is estimated at ~10 mmol/l, of which >95% is sequestered by magnesium chelators or bound to other biomolecules, including phospholipids, ribosomes and phosphonucleotides, particularly ATP and ADP (175–177). Intracellular free or ionized magnesium concentration ([Mg\(^2+\)]) is almost equal to the circulating magnesium concentration (0.5–1 mmol/l) (177). Virtually every biological process requires magnesium. Not only is it an essential cofactor for hundreds of enzymes, but it is crucial for the maintenance of the active conformation of macromolecules, the regulation of lipid- and phosphoinositide-derived second messengers, and the regulation of transporters and ion channels (175–177). Moreover, magnesium is an important modulator of [Ca\(^{2+}\)]\(_i\), a major determinant of cell contraction, proliferation, migration, and secretion (65, 67). Magnesium regulates [Ca\(^{2+}\)]\(_i\) in large part through its negative modulatory effects on numerous Ca\(^{2+}\) channels [L-type, T-type, store-operated, and calcium release-activated Ca\(^{2+}\) channels (CRAC)], by influencing Ca\(^{2+}\)-ATPase activity, and by regulating ryanodine receptors and mobilization of intracellular Ca\(^{2+}\) from reticular stores (239, 259). Intracellular magnesium is tightly regulated by precise control mechanisms at the level of magnesium entry, magnesium efflux, and intracellular buffering and compartmentalization (Fig. 1). Small changes in [Mg\(^{2+}\)]\(_i\) could lead to significant effects on signaling pathways that regulate cellular functions.

Until recently, little was known about protein transporters regulating transmembrane magnesium influx. A few magnesium transporters had been demonstrated, but only at the biophysical and functional levels. Recent advances in genetics, genomics, and proteomics have facilitated significant progress in the field, and to date, a number of genes and proteins have been identified as transmembrane magnesium transporters, with TRPM6 and TRPM7 being the best characterized.

**Magnesium influx.** Magnesium influx involves Na\(^+\)-dependent and Na\(^+\)-independent systems (Table 2). Na\(^+\)-dependent Mg\(^{2+}\) transport occurs via the putative Na\(^+\)/Mg\(^{2+}\) exchanger, whereas Na\(^+\)-independent mechanisms exchange Mg\(^{2+}\) for extracellular ions, including Ca\(^{2+}\) (Ca\(^{2+}\)/Mg\(^{2+}\) exchanger), Mn\(^{2+}\) (Mn\(^{2+}\)/Mg\(^{2+}\) antiporter), and Cl\(^-\) (Cl\(^-\)/Mg\(^{2+}\) cotransporter) (51, 53, 55, 72, 73, 125, 126). The Na\(^+\)/Mg\(^{2+}\) exchanger has been demonstrated in many cardiovascular cell types, including VSMCs and cardiomyocytes, and is regulated by multiple factors important in vascular biology and hypertension such as ANG II, vasopressin, isoproterenol, ET-1, and insulin. Cardiac Na\(^+\)/Mg\(^{2+}\) antiport stoichiometry appears to be 1 Na\(^+\):1 Mg\(^{2+}\) (8). Na\(^+\)-independent Mg\(^{2+}\) extrusion pathways have been demonstrated mainly in erythrocytes and hepatic cells, but not in vascular cells (72, 73). Magnesium efflux systems have only been demonstrated at a functional level, using pharmacological and biophysical strategies. Identification and characterization of the genes and proteins corresponding to the Na\(^+\)/Mg\(^{2+}\) antiporter and the Ca\(^{2+}\)/Mg\(^{2+}\) exchanger still await confirmation, and to date, neither of these transporters has yet been cloned.

**Mg\(^{2+}\) efflux.** Unlike other major cellular ions, including Na\(^+\), Ca\(^{2+}\), and K\(^+\), very little is known about systems that regulate Mg\(^{2+}\) efflux. Functional studies have suggested that Mg\(^{2+}\) enters cells through Mg\(^{2+}\)/anion cotransport, via countertransport pathways utilizing the electrochemical gradient of Na\(^+\), and through cation channels. There is increasing interest in Mg\(^{2+}\) channels because of the recent characterization of these channels by functional cloning. At least seven transmembrane Mg\(^{2+}\) channels have been cloned. The mitochondrial RNA splicing 2 protein (Msr2p) was the first human magnesium transporter characterized (25, 108). Numerous molecules with magnesium transport capabilities have been identified through a screen designed to discover genes upregulated under hypomagnesemic conditions, including the human solute carrier family 41, members 1 and 2 (SLC41A1, SLC41A2) channels, magnesium transporter 1 (MAGT1), and ancient conserved domain protein 2 (ACDP2) (165, 182). Some of these transporters have been identified in cardiovascular tissue (Table 3). However, the biological significance and mechanisms of regulation of these transporters have yet to be described.

Investigation of molecular causes underlying hereditary diseases associated with hypomagnesemia led to the cloning and
Table 2. Magnesium transporters involved in cellular \( \text{Mg}^{2+} \) efflux and influx

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Protein</th>
<th>Function</th>
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<tbody>
<tr>
<td>Mg(^{2+}) efflux mechanisms</td>
<td></td>
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<tr>
<td>( \text{Mg}^{2+}/\text{Mg}^{2+} ) antipporter</td>
<td></td>
<td>Exchanges ( \text{Mn}^{2+} ) for ( \text{Mg}^{2+} )</td>
</tr>
<tr>
<td>( \text{Mn}^{2+}/\text{Mg}^{2+} ) antipporter</td>
<td></td>
<td>Exchanges Ca(^{2+}) for ( \text{Mg}^{2+} )</td>
</tr>
<tr>
<td>Ca(^{2+}/\text{Mg}^{2+}) antipporter</td>
<td></td>
<td>Exchanges Sr(^{2+}) for ( \text{Mg}^{2+} )</td>
</tr>
<tr>
<td>Cl(^{-}/\text{Mg}^{2+}) cotransporter</td>
<td></td>
<td>Cotransport of Cl(^{-}) and ( \text{Mg}^{2+} )</td>
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<tr>
<td>Sr(^{2+}/\text{Mg}^{2+}) antipporter</td>
<td></td>
<td>Exchanges Sr(^{2+}) for ( \text{Mg}^{2+} )</td>
</tr>
<tr>
<td>[HCO(_3)](^{-}/\text{Mg}^{2+}) cotransporter</td>
<td></td>
<td>Cotransport of HCO(_3) and ( \text{Mg}^{2+} )</td>
</tr>
<tr>
<td>Mg(^{2+}) influx mechanisms</td>
<td></td>
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</tr>
<tr>
<td>Mitochondrial RNA splicing 2 protein</td>
<td>Mrsp</td>
<td>Mitochondrial ( \text{Mg}^{2+} ) influx</td>
</tr>
<tr>
<td>Solute carrier family 41, member 1</td>
<td>SLC41A1</td>
<td>General transporter for divalent cations</td>
</tr>
<tr>
<td>Solute carrier family 41, member 2</td>
<td>SLC41A2</td>
<td>General transporter for divalent cations, but not Ca(^{2+})</td>
</tr>
<tr>
<td>Magnesium Transporter 1</td>
<td>MagT1</td>
<td>Mg(^{2+})-specific transporter</td>
</tr>
<tr>
<td>Ancient Conserved Domain Protein 2</td>
<td>ACDP2</td>
<td>General transporter for divalent cations, but not Ca(^{2+})</td>
</tr>
<tr>
<td>Transient receptor potential melastatin 6</td>
<td>TRPM6</td>
<td>Renal and gastrointestinal ( \text{Mg}^{2+} ) absorption</td>
</tr>
<tr>
<td>Transient receptor potential melastatin 7</td>
<td>TRPM7</td>
<td>Transcellular ( \text{Mg}^{2+} ) transport, cell viability, cell adhesion, mechanotransduction, cytoskeletal organization, neurotransmitter release, immune response Paracellular ( \text{Mg}^{2+} ) and Ca(^{2+}) reabsorption in the thick ascending limb of loop of Henle</td>
</tr>
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Paracellin-1

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Protein</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRPM6</td>
<td>Kidney tubules</td>
<td>Mutations cause HSH leading to VSMC death unless ( \text{Mg}^{2+} ) supplemented; associates with TRPM7</td>
</tr>
<tr>
<td>TRPM7</td>
<td>VSMC</td>
<td>TRPM7 deficiency is lethal; negatively regulated by intracellular ( \text{Mg}^{2+} ); regulated by ANG II, aldosterone, bradykinin, stretch, and osmotic gradient</td>
</tr>
<tr>
<td>SLC41A1</td>
<td>Heart</td>
<td>Gene upregulated in hypomagnesemic conditions</td>
</tr>
<tr>
<td>SLC41A2</td>
<td>Kidney</td>
<td>Overexpression in TRPM7(^{-/-}) partially compensates for their requirement in supplemental ( \text{Mg}^{2+} )</td>
</tr>
<tr>
<td>MagT1</td>
<td>Distal convoluted tubule</td>
<td>Gene upregulated in hypomagnesemic conditions</td>
</tr>
<tr>
<td>ACDP2</td>
<td>Kidney cortex</td>
<td>Gene upregulated in hypomagnesemic conditions</td>
</tr>
<tr>
<td>Paracellin-1 (claudin 16)</td>
<td>Ascending limb, loop of Henle</td>
<td>Tight junction regulating paracellular ( \text{Mg}^{2+} ) transport; mutations cause FHHNC, with no improvement with dietary ( \text{Mg}^{2+} ) supplementation</td>
</tr>
<tr>
<td>Mrs2p</td>
<td>Inner mitochondrial</td>
<td>Regulates mitochondrial membrane potential</td>
</tr>
</tbody>
</table>

HSH, hypomagnesemia with secondary hypocalcemia; FHHNC, familial hypomagnesemia with hypercalciuria and nephrocalcinosis; VSMC, vascular smooth muscle cells.
**TRPM channels.** The melastatin-related TRP subfamily was named based on the first discovered member, melastatin 1 (TRPM1), the gene of which was identified from melanomas (47). Members of the TRPM family are divided into four groups: TRPM1/3, TRPM2/8, TRPM4/5, and TRPM6/7 (111, 113, 142, 143, 233). TRPM channels exhibit highly varying cation permeability, from Ca\(^{2+}\) impermeable (TRPM4/5) to highly Ca\(^{2+}\) and Mg\(^{2+}\) permeable (TRPM6 and TRPM7). TRPM2 is expressed mainly in the brain and is a nonselective cation channel permeable mainly to Na\(^{+}\), Ca\(^{2+}\), K\(^{+}\), and Cs\(^{+}\). It is unusual in that it has ADP-ribose pyrophosphatase activity and has an ADP-ribose hydrolase homolog at its COOH terminus. TRPM2 is activated by H\(_2\)O\(_2\), functions as a sensor of the cellular redox state, and is implicated in oxidative stress/reactive oxygen species- and TNF-\(\alpha\)-mediated Ca\(^{2+}\) influx and cell death (77, 162, 163). TRPM3 is found in kidney and brain and is a cation channel permeable to divalent cations, especially Ca\(^{2+}\) and Mn\(^{2+}\). TRPM4 exhibits the highest expression in heart, pancreas, and placenta, and TRPM5 is found in the tongue, lungs, testis, brain, and gastrointestinal tract (58). TRPM4 and TRPM5 are permeable to monovalent cations but impermeable to Ca\(^{2+}\) (50). TRPM8 is expressed in sensory nerves and the prostate and acts as a plasmalemmal Ca\(^{2+}\) channel and as an intracellular Ca\(^{2+}\) release channel. It is activated by cold temperature, by pharmacological agents evoking a “cool” sensation, such as menthol, and by androgens.

The most intriguing of the TRP channels are TRPM6 and TRPM7 (29–32, 45, 57, 58). These two proteins are structurally unique, because they are to date the only known proteins comprising an ion channel, containing a magnesium-permeable pore, fused to a kinase domain at the COOH terminus, hence termed a “chanzyme” (channel plus enzyme) (33, 34, 196–198, 234–236). TRPM7 is also a chanzyme, but instead of a kinase domain, TRPM2 possesses an ADP-ribose hydrolase homolog. TRPM6 and TRPM7 are now well accepted as important regulators of magnesium homeostasis. Their discovery was by serendipity, because when these proteins were originally cloned, it was not in a conscious effort to identify magnesium regulators. As recently detailed by Schmitz et al. (198) in an excellent review, Ryazanov (181) identified both genes in their search for homologs of eukaryotic elongation factor 2 (eEF2) kinase and called them CHAK1 (TRPM7) and 2 (TRPM6), standing for channel kinase (160, 161). At the same time, TRPM7 was isolated by two other groups: Clapham’s group (179) identified the TRPM7 kinase domain in a yeast-two-hybrid screen using the C-domain of PLC as a bait, whereas Fleig’s group (146) cloned TRPM7 using a bioinformatics approach designed to identify novel putative ion entry pathways in human lymphocytes, with a focus on calcium signaling. Under physiological conditions, TRPM7 preferentially transports magnesium and, to a lesser extent, calcium and other divalent cations. TRPM7 is ubiquitously expressed, and targeted disruption of the channel gene in cell lines is lethal, highlighting the critical role of this protein in cell physiology (3, 4). TRPM6 expression is high in kidney (distal convoluted tubule) and intestine (30–32, 234–236). Immunohistochemistry reveals...
that TRPM6 colocalizes with the Na\(^{+}/\)Cl\(^{-}\) cotransporter NCCT, as well as with parvalbumin and calbindin-D\(_{28k}\), cytosolic proteins that buffer intracellular magnesium (234–236). TRPM6 and TRPM7 share ~50% sequence homology and are constitutively active.

The homologous channels TRPM6 and TRPM7 are both essential for magnesium homeostasis and are functionally interdependent, probably due to differences in cellular and biochemical characteristics (191–198, 233). TRPM6 and TRPM7 are capable of forming homo- and heteromeric complexes (193, 194). In particular, TRPM6 forms functional homomeric channels and heteromeric TRPM6/7 channels. The three channels, TRPM6, TRPM7, and the complex TRPM6/7, are distinct ion channels that exhibit different divalent cation permeability, pH sensitivity, and unique single-channel conductance. Despite the fact that TRPM6 and TRPM7 share significant sequence identity, they have distinct properties with respect to the pharmacological agent 2-aminoethoxydiphenyl borate (2-APB). Whereas micromolar levels of 2-APB maximally increase TRPM6 activity, they significantly inhibit activity of TRPM7 channels (126). TRPM6, TRPM7, and TRPM6/7 are all involved in magnesium homeostasis and are suggested to play differential roles in regulating transmembrane Mg\(^{2+}\) transport. From a functional viewpoint, TRPM6 and TRPM7 are nonredundant, and they cannot compensate for each other’s activity (152, 153). This is evidenced by the fact that TRPM6-deficient patients are hypomagnesemic, even though TRPM7 is present and TRPM7\(^{-/-}\) cells cannot be rescued by TRPM6 overexpression (196, 198).

**Regulation of TRPM6 and TRPM7**

Factors influencing TRPM6 and TRPM7 expression and activity are still under investigation. Clapham and colleagues (33, 34) demonstrated that phosphatidylinositol 4,5-bisphosphate (PIP\(_2\)) inhibits TRPM7 channel activity, and Mubagwa et al. (144) suggested that ATP and PIP\(_2\) modulate constitutively expressed TRPM7 in cardiac cells. Fleig et al. (57) suggested that cAMP influences TRPM7 channel activity, whereas in neuroblastoma N1E-115 cells, cAMP/cGMP signaling does not seem to be involved (115). TRPM7 binds directly to several PLC isoforms, including PLC\(_{\gamma}\) and PLC\(_{\beta}\) (179), which may be important for G protein-coupled receptor activation of TRPM7. Recent studies demonstrated that humoral factors, including bradykinin, ANG II, aldosterone, and estrogen, and mechanical factors, such as shear stress, which are important in the regulation of vascular tone and structure, modulate TRPM6 and TRPM7 (78, 157, 174, 230). Bradykinin, acting through PLC-coupled receptors, increases TRPM7 channel activity in N1E-115 cells. In VSMCs, ANG II and aldosterone modulate TRPM6 and TRPM7 expression and influence TRPM7-dependent Mg\(^{2+}\) transport. Osmotic gradients also have been implicated in TRPM7 regulation (21).

The role of the kinase domain in TRPM7 regulation is still unclear. Some studies have reported that the kinase domain is critical for channel activity and gating (179, 211), whereas others reported that the kinase is not essential for channel function but that it may play a role as a modulator of channel activity (135, 196). Li et al. (127) reported that the amino acid residues E1024/E1047 and E1029/E1052 in the putative pore region of TRPM6 and TRPM7 are essential for their magnesium permeability. Most of these studies were performed in immortalized cell lines, which may explain, in part, the controversial data. Much research, especially in physiologically relevant systems and not in cell lines, is still needed to understand how TRPM7 is regulated, what the role of the kinase domain is, what stimuli activate or inhibit TRPM7 activity, how intracellular signaling molecules influence TRPM7 channel and kinase domains, what the downstream signaling targets of TRPM7 kinase are, and how TRPM7 influences cellular functional responses.

**Regulation of TRPM6 and TRPM7 by Magnesium**

TRPM7, like TRPM6, is regulated by changes in cytosolic Mg\(^{2+}\) or Mg\(^{2+}\)-ATP (43, 68, 75, 142, 143, 146, 191–198), which explains why TRPM7 and TRPM6 were previously called MIC (magnesium-inhibiting channel) or MagNuM (magnesium-nucleotide-regulated metal ion channel) (74, 75, 80, 96, 110). The inhibition of TRPM7 channels by Mg\(^{2+}\)/Mg-ATP is voltage independent. The inhibitory binding site for magnesium is unknown; it is probably not within the pore but, rather, at the level of the kinase domain, since TRPM7 kinase activity requires magnesium (79). Kinase-deleted or mutant forms of TRPM7 kinase have increased sensitivity to magnesium, whereas those with mutations removing the catalytic or autophosphorylation sites have no altered magnesium sensitivity. Magnesium nucleotides, such as Mg-ATP and Mg-GTP, have been shown to inhibit TRPM7 channels, but the inhibition has been shown to be attributable to free intracellular Mg\(^{2+}\).

Extracellular magnesium causes voltage-dependent block and also permeates TRPM6 and TRPM7 channels. The dual ability of TRPM7 to act as a channel and at the same time as a kinase suggests that this protein is involved in regulating both cellular magnesium status and intracellular signaling pathways underlying cellular function (160). The fact that these channels conduct Mg\(^{2+}\) and at the same time are Mg\(^{2+}\)-sensitive provides an important feedback mechanism regulating magnesium homeostasis. Intracellular magnesium inhibits TRPM7, which may serve as a negative signal to reduce further magnesium uptake when the cell has sufficient magnesium. Under conditions of low [Mg\(^{2+}\)], recovery from this inhibition may open the channel to normalize cytosolic Mg\(^{2+}\) levels.

**TRPM6 and TRPM7 Kinase as Signaling Molecules**

The kinase domain of TRPM6 and TRPM7 bears sequence similarity to eEF2 serine/threonine kinases and other proteins, which contain an \(\alpha\)-kinase domain. Of the divalent metal ions, only changes in [Mg\(^{2+}\)], can directly influence the enzymatic activity of TRPM7 kinase (181). TRPM6 and TRPM7 can autophosphorylate. TRPM7 kinase contains two serine residues that undergo self-phosphorylation, Ser\(^{1551}\) and Ser\(^{1567}\) (134, 196–198). Whereas TRPM6 can phosphorylate TRPM7, thereby potentiating TRPM7 channel activity, the opposite is not true, indicating that despite their homology, these kinases have differential substrate specificity (196, 197). This was demonstrated in DT40 cells containing a loss-of-function mutation in the TRPM7 gene that was not rescued by TRPM6 (196, 197).

To date, three known TRPM7 kinase substrates have been identified: annexin-1 (46), myosin IIA heavy chain (35), and calpain (208) (Fig. 4). Annexin-1 (ANXA1) is a Ca\(^{2+}\)- and
phospholipid-binding protein that is an endogenous modulator of inflammation (255). TRPM7 phosphorylates annexin-1 on Ser5, but the biological significance of this remains unclear (46). Myosin II heavy chain is involved in cell migration, cell growth, apoptosis, and cytoskeletal organization. Calpain protease is implicated in the control of cell adhesion through focal adhesion disassembly (216). The biological significance of TRPM7-regulated annexin-1, myosin II heavy chain, and calpain remains unclear, since studies on these substrates were performed in cell lines. Nevertheless, taking these findings together, TRPM7 kinase is emerging as a signaling molecule important in regulating fundamental cellular functions (32). This is further substantiated by the findings that TRPM7 knockout in mice is embryonically lethal (Ryazanov AG, personal communication) and that TRPM7−/− cells die (1, 2, 84, 140).

TRPM6 and TRPM7 as Regulators of Magnesium Homeostasis

The importance of TRPM6 in the regulation of whole body Mg2+ was first identified in patients who presented with hypomagnesemia with secondary hypocalcemia (HSH) due to defective Mg2+ reabsorption in the kidney (29–32, 191–195, 198, 234, 238). Hypocalcemia in HSH is secondary to low serum Mg2+ resulting from inhibition of parathyroid hormone production. These patients were found to have loss-of-function mutations in the TRPM6 gene (29–32, 191–195). A TRPM7 variant has recently been described in patients with Guamanian amyotrophic lateral sclerosis (ALS-G) and parkinsonism dementia (PD-G) (79).

Despite the high homology of TRPM6 and TRPM7 and the fact that both are implicated in Mg2+ distribution in the body, they have physiologically and pharmacologically distinct roles in Mg2+ homeostasis (109, 126, 192). Whereas TRPM6 appears to be primarily involved in regulating total body Mg2+ levels through the kidney and gastrointestinal systems, TRPM7 may be more important in regulating intracellular Mg2+ homeostasis and [Mg2+]i in a cell-specific manner (161–163, 251). The exact role of TRPM6/TRPM7 complex in Mg2+ homeostasis remains to be elucidated.

Cellular Functions of TRPM7

TRPM7 plays a role in cell death (1, 2, 56, 89, 137, 138, 140) and was recently shown to be important in cell cycle regulation (76, 213). TRPM7 and [Mg2+]i regulate p27Kip1, an inhibitor of the cyclin E-dependent regulator of the G1-S transition in the cell cycle. My group (225–227) demonstrated in VSMCs that magnesium inhibits p27Kip1 expression and activity and that it promotes cell cycle progression. TRPM7 also is present in synaptic vesicles and may be involved in acetylcholine release (142). TRPM7 also is found in immune cells and, together with other TRPM family members, has been implicated in modulating the immune response (133, 163). Through its effects on myosin IIA heavy chain and calpain, TRPM7 may be involved in regulating vascular cell adhesion, migration, and contraction (35, 208). It also has been implicated to play a role in mechanotransduction, important in the regulation of vascular function (155–157, 207).

TRPM6 and TRPM7 in the Vasculature

Very little is known about TRPMs in vascular cells. My group (78, 230) and others (234–236, 238) have demonstrated that VSMCs from mouse, rat, and human resistance arteries possess TRPM6 and TRPM7 cation channels and that TRPM7 is critically involved in regulating magnesium influx. TRPM7 also has been identified in vascular cells from aorta and pulmonary arteries (255). My group (78, 230) showed that ANG II and aldosterone regulate vascular TRPM7 acutely by inducing phosphorylation and chronically by increasing expression at the mRNA and protein levels. Downregulation of vascular TRPM7 by small interference (si)RNA reduced basal [Mg2+]i and ANG II-stimulated [Mg2+]i transients and attenuated ANG II-mediated VSMC growth. These findings confirmed that TRPM7 is a key regulator of magnesium homeostasis and that it plays a major role in cell growth (78, 230). Two
recent studies in cancer cells and osteoblasts further support the importance of TRPM7 in ion homeostasis and cell proliferation (3, 89).

Oancea et al. (157) showed that fluid flow stimulates cytosol-to-membrane translocation of TRPM7 in VSMCs and that fluid-induced shear stress increases the amplitude of a native TRPM7-like current. These provocative findings suggested that TRPM7 may act as a mechanotransducer, which could be important in pathological responses to vessel wall injury, particularly in the context of endothelial damage. Signaling molecules involved in this process are unknown, but cytoskeletal elements may be important. Potential candidates could be calpain and myosin IIA heavy chain, because they are cytoskeleton-associated proteins and are both TRPM7 kinase-sensitive substrates.

**Magnesium Transporters, TRPM6, TRPM7, and the Vasculature in Hypertension**

Studies from my laboratory have demonstrated that decreased [Mg^{2+}], in hypertension is associated with alterations in both Mg^{2+} influx and influx (Fig. 5). My group (221, 223, 225–227) and others (1, 25, 64) have shown that the Na^{+}/Mg^{2+} antiport plays a major role in Mg^{2+} extrusion in cardiac, renal, and vascular smooth muscle cells and that in hypertension, the Na^{+}/Mg^{2+} antipoter function is altered. This exchange is inhibited by amiloride, quinidine, imipramine, and manganese (72, 73, 175, 176). In SHR, administration of amiloride and quinidine was associated with an increase in vascular [Mg^{2+}], and attenuated development of hypertension (225–227). In ANG II-induced hypertension in rats, inhibition of the Na^{+}/Mg^{2+} antiporter resulted in reduced blood pressure, normalization of vascular and renal MAP kinase activity, and improved vascular structure (225–227). Other studies also have demonstrated alterations in Na^{+}/Mg^{2+} exchanger activity in hypertension (104, 105, 164).

Altered magnesium influx in VSMCs in SHR was associated with downregulation of vascular TRPM7 but not of TRPM6 (230). Mechanisms underlying this may relate to 1) modulation of TRPM7 by ANG II and other vasoactive agents important in blood pressure regulation, 2) alterations in TRPM7 gene/protein expression, and/or 3) dysregulation of intracellular Mg^{2+} homeostasis. My group (206) recently found that mice infused with aldosterone exhibit cardiovascular and renal remodeling, fibrosis and inflammation, and associated downregulation of renal TRPM7. Magnesium supplementation ameliorated some of these responses. Similar to what was reported in cell lines, we found that TRPM7 and Mg^{2+} are critical for

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![Figure 5. Magnesium transport mechanisms that may be altered in VSMCs in hypertension. Decreased Mg^{2+} influx, due to reduced TRPM7 expression/activity and decreased diffusion across cell membrane, lead to reduced intracellular levels of Mg^{2+}. Vasoactive agents, including ANG II, ET-1, bradykinin, and aldosterone, and mechanical factors, such as shear stress, stretch, and pressure, modulate VSMC TRPM7 expression and activity. Increased Mg^{2+} efflux due to increased activation of Na^{+}-dependent and Na^{+}-independent exchangers also may contribute to reduced intracellular Mg^{2+} levels in hypertension. Changes in [Mg^{2+}] influence multiple signaling molecules and enzymes, including mitogen-activated protein kinases (MAPK), protein tyrosine kinases, cell cycle proteins, and transcription factors. Alterations in [Mg^{2+}], also influence intracellular Ca^{2+} homeostasis. In general, Mg^{2+} antagonizes Ca^{2+} actions. ↑, increase; ↓, decrease; GPCR, G protein-coupled receptor; PLC, phospholipase C.

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**Table 4. Tools currently used to investigate TRPM6 and TRPM7 status**

<table>
<thead>
<tr>
<th>Parameter Assessed</th>
<th>Methodology</th>
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<tbody>
<tr>
<td>Electrophysiological characteristics</td>
<td>Patch clamp</td>
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<tr>
<td>mRNA expression</td>
<td>RT-PCR</td>
</tr>
<tr>
<td>Protein expression/content</td>
<td>Western blotting</td>
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<tr>
<td>Protein distribution</td>
<td>Immunocytochemistry</td>
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<tr>
<td>Mg^{2+}, Ca^{2+} transport</td>
<td>Fluoroprobes</td>
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<tr>
<td>TRPM6 activation</td>
<td>2-APB*</td>
</tr>
<tr>
<td>TRPM7 inhibition</td>
<td>2-APB*</td>
</tr>
<tr>
<td>TRPM6, TRPM7 channel inhibition</td>
<td>Gd^{3+}</td>
</tr>
<tr>
<td>TRPM6, TRPM7 knockdown</td>
<td>siRNA</td>
</tr>
</tbody>
</table>

*Micromolar levels of 2-aminoethoxydiphenyl borate (2-APB) maximally increase TRPM6 but significantly inhibit TRPM7 channel activities, whereas millimolar concentrations of 2-APB potentiate TRPM6 and TRPM7 channel activities (126). RT-PCR, reverse transcriptase-polymerase chain reaction; qPCR, quantitative PCR; 2-APB; siRNA, small interfering RNA.
VSMC viability, because TRPM7 knockdown with siRNA resulted in arrested cell growth, which was restored upon Mg2+ supplementation (78). Hence aberrations in cellular magnesium homeostasis and altered TRPM7 expression/activity may contribute to VSMC proliferation, inflammation, fibrosis, and contraction, important in processes involved in vascular remodeling in hypertension (Fig. 5).

Clinical Relevance of TRPM6, TRPM7, Hypomagnesemia, and Hypertension

Clinically, there are a number of well-defined conditions where hypertension is associated with hypomagnesemia, including hyperaldosteronism, use of diuretics in the management of hypertension and congestive cardiac failure, and treatment with calcineurin inhibitors as immunosuppressive drugs (11, 180). Recent evidence implicates alterations in TRPM6 and TRPM7 in these conditions. My group demonstrated that aldosterone modulates vascular TRPM6 and TRPM7 expression/activity (206, 230). In patients with congestive cardiac failure and hyperaldosteronism, spironolactone, a mineralocorticoid receptor blocker, reduced arrhythmias and prevented intraerythrocyte magnesium depletion, possibly through effects on cellular magnesium transport systems (63). Use of diuretics, particularly thiazides and furosemide, in the management of hypertension or congestive cardiac failure is also associated with hypomagnesemia (37, 149–151). In an animal model of thiazide-induced hypomagnesemia and in Na+/Cl− cotransporter (NCC) knockout mice, an animal model of Gitelman syndrome characterized by hypomagnesemia, epithelial TRPM6 expression and activity were reduced. Hence, TRPM6 downregulation may represent a general mechanism involved in the pathogenesis of hypomagnesemia associated with diuretics and NCC inhibition or inactivation (149–151). Calcineurin inhibitors, including cyclosporin A and tacrolimus, induce hypomagnesemia as well as hypertension (147). Processes by which this occurs are unclear, but altered cellular magnesium transport may be important. In rats, tacrolimus infusion induced renal Mg2+ wasting by downregulating TRPM6 (149–151). In proximal tubular cells, cyclosporine reduced paracellin-1 expression and paracellular magnesium transport, which might contribute to renal magnesium wasting in the cyclosporine-mediated tubular actions (27). Although the biological importance of TRPM6- and TRPM7-regulated Mg2+ transport is becoming increasingly apparent, and there is some evidence that TRPM6 is involved in hypomagnesemia associated with renal disease, the exact role of TRPM6 and TRPM7 in cardiovascular physiology and pathology still awaits clarification.

Conclusions

Emerging evidence indicates that low magnesium may play a pathophysiological role in the development of hypertension. Magnesium normally regulates vascular tone and reactivity by modulating Na+, K+, and Ca2+ and by influencing activity of multiple enzymes. At the vascular level, decreased Mg2+ is associated with endothelial dysfunction, increased reactivity, enhanced contractility, vascular remodeling and inflammation, and elevated blood pressure. On the other hand, increased vascular Mg2+ levels are associated with vasodilation, anti-inflammatory responses, and reduced blood pressure. Because of the importance of Mg2+ in biological processes, its intracellular concentration and transmembrane transport are tightly controlled. Until recently, very little was known about transporters regulating Mg2+ transport. To date, a number of Mg2+-efflux pathways, including the Na+/Mg2+ antiporter and the Ca2+/Mg2+ exchanger, have been demonstrated at a functional level. These transporters have not yet been identified at the gene/protein levels. Mg2+ influx occurs through various channels, of which the best characterized and most recently cloned are TRPM6 and TRPM7. These cation channels are unique in that they contain a channel and a kinase domain; hence they are termed chanzymes. Na+/Mg2+ exchanger activity and TRPM7 expression/activity appear to be altered in experimental models of hypertension. Such aberrations may contribute to Mg2+ dysregulation in hypertension. Since the recent identification and characterization of Mg2+-selective transporters, there has been enormous interest in the field. However, there is still a paucity of information, and much research is needed to clarify the exact mechanisms of Mg2+ regulation in the cardiovascular system and the implications of aberrant transmembrane Mg2+ transport in the pathogenesis of hypertension. Moreover, the exact role(s) of TRPM6 and TRPM7 in the pathophysiology of cardiovascular disease awaits further clarification.

The field of TRPM6 and TRPM7 is still young, and the tools to fully characterize these cation channels have not yet been fully developed. To date, most studies have relied on electrophysiological approaches, molecular and genetic manipulation of the genes and proteins, pharmacological strategies, and expression profiles (Table 4). Once more specific and sensitive tools become available, the (patho)physiological significance of these unique channels will become apparent. There is still much to be discovered regarding the function and regulation of TRPM6, TRPM7, and TRPM6/7 and of the biological importance of these channels in cardiovascular tissue. Identification of downstream molecular targets of the kinase domain of these chanzymes will help elucidate the functional significance in different cell types. Genetic association studies will provide further insights into the role of TRPM6, TRPM7, and TRPM6/7 in the pathogenesis of (cardiovascular) disease. New molecular tools and transgenic and knockout animals will certainly facilitate our understanding of the critical (patho)physiological roles of these ion channels. Future research in the field is certainly challenging but with great potential in uncovering new mechanisms underlying hypertension and other vascular disease.

GRANTS

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Invited Review

TRPM, MAGNESIUM, VESSELS, AND HYPERTENSION


