Divalent Cation Metabolism: Magnesium

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Magnesium is an essential intracellular cation. Nearly 99% of the total body magnesium is located in bone or the intracellular space. Magnesium is a critical cation and cofactor in numerous intracellular processes. It is a cofactor for adenosine triphosphate; an important membrane stabilizing agent; required for the structural integrity of numerous intracellular proteins and nucleic acids; a substrate or cofactor for important enzymes such as adenosine triphosphatase, guanosine triphosphatase, phospholipase C, adenylate cyclase, and guanylate cyclase; a required cofactor for the activity of over 300 other enzymes; a regulator of ion channels; an important intracellular signaling molecule; and a modulator of oxidative phosphorylation. Finally, magnesium is intimately involved in nerve conduction, muscle contraction, potassium transport, and calcium channels. Because turnover of magnesium in bone is so low, the short-term body requirements are met by a balance of gastrointestinal absorption and renal excretion. Therefore, the kidney occupies a central role in magnesium balance. Factors that modulate and affect renal magnesium excretion can have profound effects on magnesium balance. In turn, magnesium balance affects numerous intracellular and systemic processes [1–12].

In the presence of normal renal function, magnesium retention and hypermagnesemia are relatively uncommon. Hypermagnesemia inhibits magnesium reabsorption in both the proximal tubule and the loop of Henle. This inhibition of reabsorption leads to an increase in magnesium excretion and prevents the development of dangerous levels of serum magnesium, even in the presence of above-normal intake. However, in familial hypocalciuric hypercalcemia, there appears to be an abnormality of the thick ascending limb of the loop of Henle that prevents excretion of calcium. This abnormality may also extend to Mg. In familial hypocalciuric hypercalcemia, mild hypermagnesemia does not increase the renal excretion of magnesium. A similar abnormality may be caused by lithium [1,2,6,10]. The renal excretion of magnesium also is below normal in states of hypomagnesemia, decreased dietary magnesium, dehydration and volume depletion, hypocalcemia, hypothyroidism, and hyperparathyroidism [1,2,6,10].

CHAPTER 4

Magnesium Distribution

TOTAL BODY MAGNESIUM (MG) DISTRIBUTION

Location	Percent of Total	Mg Content, mmol*	Mg Content, mg*
Bone	53	530	12720
Muscle	27	270	6480
Soft tissue	19.2	192	4608
Erythrocyte	0.5	5	120
Serum	0.3	3	72
Total		1000	24000

*data typical for a 70 kg adult

FIGURE 4-1

Total distribution of magnesium (Mg) in the body. Mg (molecular weight, 24.305 D) is predominantly distributed in bone, muscle, and soft tissue. Total body Mg content is about 24 g (1 mol) per 70 kg. Mg in bone is adsorbed to the surface of hydroxyapatite crystals, and only about one third is readily available as an exchangeable pool. Only about 1% of the total body Mg is in the serum and interstitial fluid [1,2,8,9,11,12].

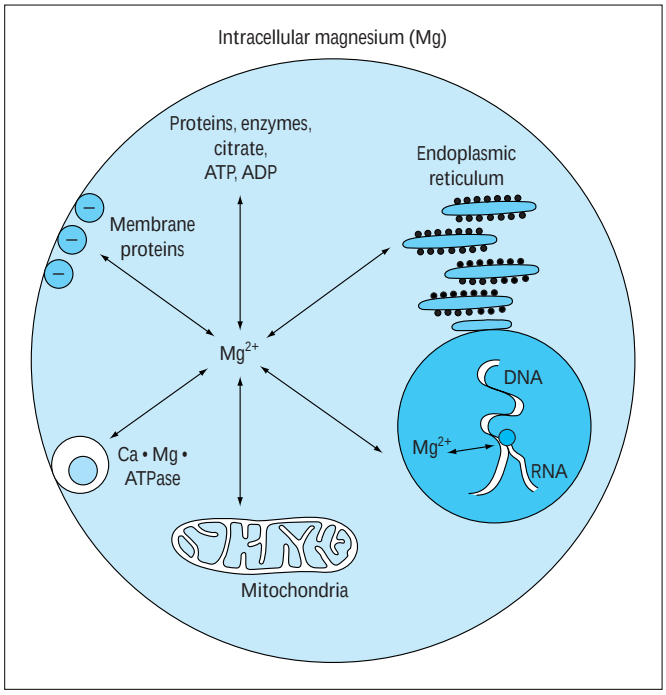

FIGURE 4-2

Intracellular distribution of magnesium (Mg). Only 1% to 3% of the total intracellular Mg exists as the free ionized form of Mg, which has a closely regulated concentration of 0.5 to 1.0 mmol. Total cellular Mg concentration can vary from 5 to 20 mmol, depending on the type of tissue studied, with the highest Mg concentrations being found in skeletal and cardiac muscle cells. Our understanding of the concentration and distribution of intracellular Mg has been facilitated by the development of electron microprobe analysis techniques and fluorescent dyes using microfluorescence spectrometry. Intracellular Mg is predominantly complexed to organic molecules (*eg*, adenosine triphosphatase [ATPase], cell and nuclear membrane-associated proteins, DNA and RNA, enzymes, proteins, and citrates) or sequestered within subcellular organelles (mitochondria and endoplasmic reticulum). A heterogeneous distribution of Mg occurs within cells, with the highest concentrations being found in the perinuclear areas, which is the predominant site of endoplasmic reticulum. The concentration of intracellular free ionized Mg is tightly regulated by intracellular sequestration and complexation. Very little change occurs in the concentration of intracellular free Mg, even with large variations in the concentrations of total intracellular or extracellular Mg [1,3,11]. ADP—adenosine diphosphate; ATP—adenosine triphosphate; Ca^{+}—ionized calcium.

Intracellular Magnesium Metabolism

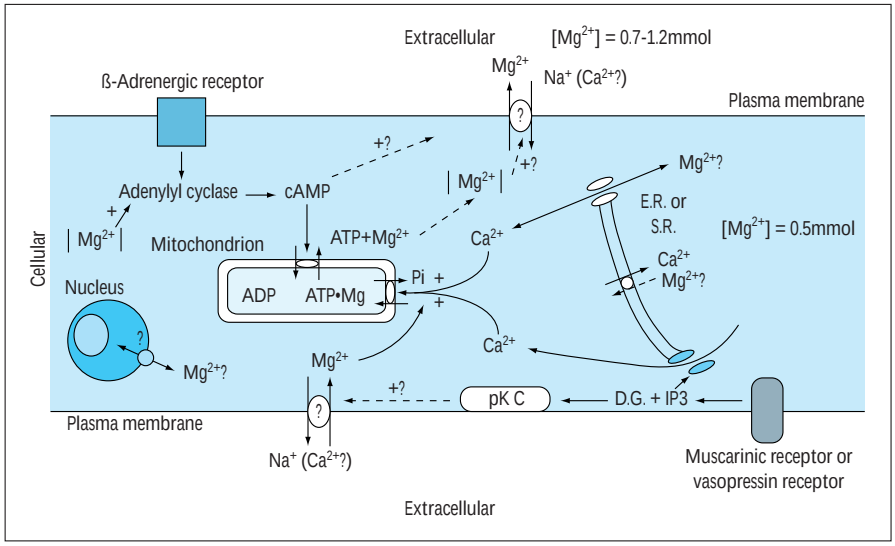

FIGURE 4-3

Regulation of intracellular magnesium (Mg^{2+}) in the mammalian cell. Shown is an example of Mg^{2+} movement between intracellular and extracellular spaces and within intracellular compartments. The stimulation of adenylate cyclase activity (*eg*, through stimulation of β-adrenergic receptors) increases cyclic adenosine monophosphate (cAMP). The increase in cAMP induces extrusion of Mg from mitochondria by way of mitochondrial adenine nucleotide translocase, which exchanges 1 Mg^{2+}-adenosine triphosphate (ATP) for adenosine diphosphate (ADP). This slight increase in cytosolic Mg^{2+} can then be extruded through the plasma membrane by way of a Mg-cation exchange mechanism, which may be activated by either cAMP or Mg. Activation of other cell receptors (*eg*, muscarinic receptor or vasopressin receptor) may alter cAMP levels or produce diacylglycerol (DAG). DAG activates Mg influx by way of protein kinase C (pK C) activity. Mitochondria may accumulate Mg by the exchange of a cytosolic Mg^{2+}-ATP for a mitochondrial matrix Pi molecule. This exchange mechanism is Ca^{2+}-activated and bidirectional, depending on the concentrations of Mg^{2+}-ATP and Pi in the cytosol and mitochondria. Inositol 1,4,5-trisphosphate (IP3) may also increase the release of Mg from endoplasmic reticulum or sarcoplasmic reticulum (ER or SR, respectively), which also has a positive effect on this Mg^{2+}-ATP-Pi exchanger. Other potential mechanisms affecting cytosolic Mg include a hypothetical Ca^{2+}-Mg^{2+} exchanger located in the ER and transport proteins that can allow the accumulation of Mg within the nucleus or ER. A balance must exist between passive entry of Mg into the cell and an active efflux mechanism because the concentration gradient favors the movement of extracellular Mg (0.7–1.2 mmol) into the cell (free Mg, 0.5 mmol). This Mg extrusion process may be energy-requiring or may be coupled to the movement of other cations. The cellular movement of Mg generally is not involved in the transepithelial transport of Mg, which is primarily passive and occurs between cells [1–3,7]. (*From* Romani and coworkers [3]; with permission.)