

Handbook of Metal-Ligand Interactions in Biological Fluids

Bioinorganic Medicine

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edited by
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Part 2, Chapter 4
Section A

INTERRELATIONS BETWEEN MAGNESIUM AND CALCIUM

by

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I. INTRODUCTION

Calcium (Ca) and magnesium (Mg) have reciprocal effects in a wide variety of functions. Their imbalance - whether caused by excess intake of one with inadequate intake of the other, or whether caused by nutrients or drugs that enhance the absorption or cause loss of one over that of the other - can induce dysfunctions and pathologic changes. It is possible to focus on interactions of Ca and Mg, alone, only under controlled (usually in vitro) laboratory conditions in which concentrations of each is varied separately, a situation far from comparable to the whole animal or clinical situation. These two cations affect each other not only directly, but through their effects on the parathyroids and response to parathyroid hormone (PTH), on calcitonin (CT), and on vitamin D metabolism. In addition, the amount present of nutrients such as phosphates, fiber and fat, as well as other vitamins, affect the utilization, distribution, and changes caused by excess and/or deficiency of Ca and Mg. At present, there is enthusiasm for increasing Ca intake as prophylaxis against some chronic diseases. A recent epidemiologic study of the dietary intakes of an elderly population disclosed that in those with high Ca-intakes, their self-selected diets were also high in Mg and other important nutrients, and that therefore those postulating a protective role for Ca on the basis of epidemiologic studies need to consider the multicollinearity in the Western diet (Holbrook and Barrett-Connor, 1991).

Mg is predominantly an intracellular (ic) cation, in which all but 1% of the body Mg is found and as which it plays vital roles in numerous cellular processes: ribosomal, mitochondrial, enzymatic - in energy metabolism, protein synthesis, new tissue formation, potassium (K) transport, Ca utilization, membrane stability, muscle contractility, cardiovascular, renal, and bone physiology and structure, and nerve impulse transmission (Aikawa, 1981; Wacker, 1980). The less than 1% of extracellular Mg that is not bound participates principally in neuromuscular transmission (Chutkow, 1971; 1980), and inhibits intravascular coagulation (Seelig, 1980; 1990). Mobilization of bone Ca usually provides the Ca required for blood coagulation, transmission of nerve impulses, neuromuscular excitability, muscle contractility, and enzyme activation, when Ca needs exceed intake, or to compensate for losses.

The low limit of the range of occidental dietary supply of Ca (400 to 1300 mg/day) is inadequate to meet the needs for normal bone formation of girls and women who are subject to bone loss at the menopause (Avioli, 1988). Dietary surveys have indicated that their Ca intake commonly falls below the recommended dietary allowance (RDA) of 1200 mg/day (Nat. Res. Council-RDA, 1989; U.S. Dept. H.E.W., 1977). Whether as much as 1200 mg/day is needed to ensure increasing bone mass in adolescent girls and young women is not certain, half to two thirds having been adequate (Lichton, 1989; Anderson and Metz, 1993). Bringing the intake up to 1.5 g/day for postmenopausal women (Hotzel and Zittermann, 1989), in view of the low occidental Mg intake, causes an imbalanced Ca/Mg ratio (Seelig, 1990). Dietary surveys have indicated that the customary intake of Mg is often below 300 mg (Abdulla et al., 1989; Lakshmanan et al., 1984; Morgan and Stampley, 1988; Morgan et al., 1985; Pennington et al., 1989; USDA, 1980), providing less than 5 mg/kg/day. This brings the dietary Ca/Mg ratio to about 4/1. At a 2 g Ca/day intake, as has been advised for pregnant and lactating women (Duggin et al., 1974; Nordin, 1986), the ratio would be 6/1 or more. It is of interest that the extensive 1932 study of Ca, Mg and phosphorus (P) gave 600 mg/day as the recommended Mg intake with a Ca/Mg ratio of 2/1 (Schmidt and Greenberg, 1935), a ratio that was long considered suitable. It is provocative that as the dietary intake in urban Japan has risen to approximately that in the occident with a rise also in the Ca/Mg ratio, cardiovascular disease has become more prevalent (Kimura et al., 1989).

The early extensive Mg balance studies of normal young adults have shown that at Mg intakes below 5 mg/kg/day, negative Mg and Ca balances are likely (Hathaway, 1962; Seelig, 1964). On Mg intake of less than 5 mg/kg/day, Mg balances were either negative or in bare equilibrium at Ca intakes of about 1 g/day. At 5-6 mg/kg/day of Mg, Ca intakes below 1 g/day allowed for positive Mg balances that were reduced in degree at Ca intakes above 1 g/day (Seelig, 1964; 1971 (Fig. 1)). A more recent study with eight healthy young women ingesting the RDA for Mg and Ca, supplemented with 1.5 g Ca/day, resulted in increased fecal and urinary Mg of 140 mg/4 days and 30 mg/4 days, respectively (Spiller et al., 1988). At Mg intakes of under 305 mg/day and Ca intakes of slightly over 1 g/day (Ca/Mg ratio of almost 4/1), the Mg balances of healthy young women remained strongly

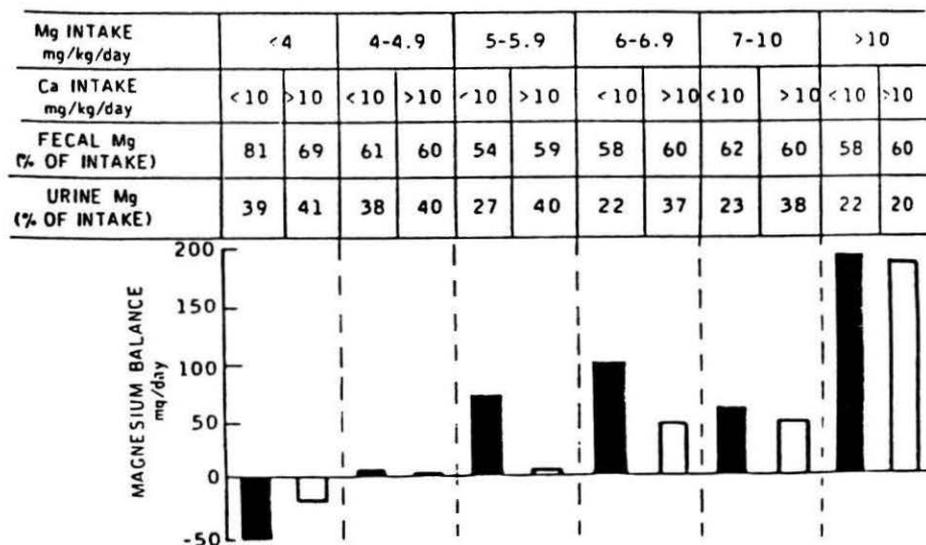


Figure 1.

Influence of calcium intake on magnesium balance in normal adults. From Seelig (1993).

difficult to interpret, since it may reflect either deposition in bone, or as soft tissue calcinosis (characteristic of Mg deficiency). A metabolic balance study of an elderly and two middle-aged men recovering from alcoholism, and an elderly woman with rheumatoid arthritis with probable Mg deficiency, all of whom were on high-Ca intake of 2 g/day, showed increased Mg and Ca retention after receiving Mg supplements of 1 g/day for three weeks (Briscoe and Ragan, 1966). Two metabolic balance studies of patients with osteopathies and/or hypercalciuria, whose Mg intakes were below 300 mg/day, showed that Ca supplementation intensified their negative Mg balances (Parlier et al., 1963; Amiot et al., 1968). Another patient with osteoporosis, whose daily Mg intake was higher (334 mg/day) and whose Mg balance was positive (+33 mg), responded to increased Ca intake (2 g/day) by reduction of Mg retention to bare equilibrium (Heaton et al., 1964).

B. Laboratory animal data

Since close to 99% of the body's Ca is in the skeleton (Avioli, 1988), inadequacies of its intake are reflected by growth failure, bone demineralization and bone loss. The manifestations of Mg deficiency, which differ by species, might be partially explained by the different Ca/Mg ratios of two species with disparate findings. Rats fed Mg-deficient diets are usually kept on their customary high-Ca diets to meet their growth requirements. Those not Mg deficient enough to die early in convulsions or of arrhythmia develop hypomagnesemia, and hypercalcemia and soft tissue calcinosis - with damage to arteries, heart and kidneys, not unlike that seen in children with hyperreactivity to vitamin D (see Chapter 5-A in Seelig, 1969). Ruminants consume forage that is not rich in Ca, and develop hypomagnesemia and hypocalcemia, which results in neuromuscular irritability (vide infra).

III. ABSORPTION AND EXCRETION OF MAGNESIUM AND CALCIUM

A. Intestinal absorption

Interrelations have been demonstrated between Mg and Ca absorption (Aikawa, 1965). With low-Mg intake, the proximal portion of the small intestine in rats exhibited increased Ca absorption - suggesting a common intestinal transport mechanism for Ca and Mg (Alcock and MacIntyre, 1962), one that might be shared also by strontium (Hendrix et al., 1963). When the intestinal Mg content was increased to above normal levels, Ca absorption was inhibited (Kessner and Epstein, 1966). Mg is actively transported in the intestine; in the terminal ileum, where Ca was secreted, Mg was absorbed by a vitamin-D independent mechanism (Hardwick et al., 1988; Karch and Rummel, 1990). Most studies of Mg absorption suggest that Mg is absorbed predominantly in the distal intestine. There is evidence, both in animals and humans, for a saturable component of Mg absorption in the small intestine and descending colon that is important at low dietary Mg intakes (Hardwick et al., 1991). Increasing the Mg intake from suboptimal amounts has improved Ca absorption (Larvor et al., 1964; Clark, 1969). Zinc intake also influences the excretory pattern of Mg and Ca (Forbes, 1961). It has been demonstrated in several species that high intestinal Ca content interferes with Mg absorption, causing conditioned Mg deficiency. It has recently been shown that the intestinal (brush border) saturable uptake of Ca is carrier-mediated, and that it is inhibited competitively by Mg and by strontium, as is the nonsaturable electrostatic binding of Ca to the intestinal membrane (Schedl et al., 1990). Increased intestinal absorption of Ca, which predisposes to hypercalcemia when associated with Mg deficiency, has long been known to lead to metastatic calcification (Hendrix et al., 1963; Kessner and Epstein, 1966). A recently demonstrated inhibitory effect of Ca on taurine uptake by rabbit intestinal brush-border membrane vesicles (Miyamoto et al., 1990) might also be related to Mg deficiency, since it is postulated that taurine is a Mg-sparing substance (Durlach and Durlach, 1984).

B. Urinary excretion

One of the earliest papers on the interrelations between Ca and Mg was the report that infusion of Mg salts increases urinary excretion of Ca (Mendel and Benedict, 1909). It was

difficult to interpret, since it may reflect either deposition in bone, or as soft tissue calcinosis (characteristic of Mg deficiency). A metabolic balance study of an elderly and two middle-aged men recovering from alcoholism, and an elderly woman with rheumatoid arthritis with probable Mg deficiency, all of whom were on high-Ca intake of 2 g/day, showed increased Mg and Ca retention after receiving Mg supplements of 1 g/day for three weeks (Briscoe and Ragan, 1966). Two metabolic balance studies of patients with osteopathies and/or hypercalciuria, whose Mg intakes were below 300 mg/day, showed that Ca supplementation intensified their negative Mg balances (Parlier et al., 1963; Amiot et al., 1968). Another patient with osteoporosis, whose daily Mg intake was higher (334 mg/day) and whose Mg balance was positive (+33 mg), responded to increased Ca intake (2 g/day) by reduction of Mg retention to bare equilibrium (Heaton et al., 1964).

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later shown that infusions of either a Ca or Mg salt increases the urinary output of the other cation (Samiy et al., 1960). Acute intravenous (iv) loading of dogs with Ca has increased renal excretion of Mg significantly (Wallach and Carter, 1961; Charbon and Hoekstra, 1962). Contributory to the Ca-induced increased Mg excretion might be the resultant increase in ultrafiltrable serum Mg, caused by binding of Ca to plasma proteins (Wallach et al., 1966). Patients with bone-losing diseases have responded to iv Ca infusion by increased urinary Mg and falls in serum (Keck et al., 1980). Mechanisms involved in interactions in renal excretion of Ca and Mg have been reviewed in detail (Massry and Coburn, 1973; Massry, 1981; Quamme, 1986). The reabsorption of Mg occurs throughout the nephron with most of filtered Mg reabsorbed by the proximal tubule and the ascending limb of the loop of Henle, which is also true for Ca. The tubular reabsorption of both Ca and Mg is so effective that 0.5-1.0% of the Ca filtered through the glomerulus (about 11 g/day) and 3-5% of the filtered Mg (1.8 g/day) is excreted in the urine (Massry and Coburn, 1973). There is a maximum tubular reabsorptive capacity for Mg (TmMg), but not for Ca (Massry and Coburn, 1973), which when lowered transiently or permanently, causes hypomagnesemia (Parfitt, 1980).

Supplementation of marginally Mg-deficient older woman with an amount of boron equivalent to that provided in a diet rich in fruits and vegetables has been shown to diminish urinary loss of Mg and Ca (Nielsen et al., 1987).

The hormones that affect bone metabolism: PTH, CT, and vitamin D metabolites, and the effect of Mg deficiency on their release and activity (Fatemi et al., 1991) (considered elsewhere in this volume) affect tubular reabsorption and thus their urinary excretion. New data have expanded our understanding of mechanisms by which renal handling of Ca and Mg are controlled. In water diuresed rats given a prostacycline (PGI)-inhibitor, the fractional excretion of both Ca and Mg declined about half (Roman et al., 1984). A Ca-channel blocker prevented the renal blood flow reduction and increased blood pressure produced by endothelin (ET-1) in normotensive rats (Madeddu et al., 1990). Synthesis of PGI, which counteracts the vasoconstrictor effects of norepinephrine in the kidney, is increased by renal ischemia (Dunn, 1989). Differential renal excretion studies in hypertensive patients disclosed that ischemic kidneys reabsorb more Na and Ca than Mg and K (Parfitt and Lukin, 1968). Either Ca-channel blockade or PGI-inhibition prevented Mg infusion-induced decline in blood pressure and increased renal blood flow in normal volunteers (Nadler et al., 1987).

IV. PLATELET- AND ENDOTHELIAL-DERIVED FACTORS, CALCIUM AND MAGNESIUM

Recent work on effects of platelet- and endothelial-derived substances indicates additional ways in which Ca and Mg exert antagonistic effects. From platelets are derived PGI₁, with vasodilator and anti-platelet aggregating properties, and thromboxane (TXB), with vasoconstrictor and platelet clumping properties. The endothelium produces several substances, three of which are considered here: the endothelial derived relaxing factor (EDRF), which has been identified as nitric oxide (NO), as well as PGI, and ET-1, that is vasoconstrictive and enhances platelet aggregation. Synthesis of and mediation by PGI is Mg dependent (Nadler et al., 1987; Nigam et al., 1986). PGI mediates, at least in part, the vasodilatory effects of infused Mg (Woods, 1991). In its absence, PGI-induced relaxation in isolated rat aortic strips is prevented (Altura et al., 1980). PGI and Mg infusions elicit similar hemodynamic effects (Bergman et al., 1981), and in vitro exposure of (umbilical) vascular endothelial cells to vasodilating concentrations of Mg stimulates release of PGI (Watson et al., 1986; Briel et al., 1987). The production of TXB has been shown to be increased by chronic Mg deficiency in rats, as was PGI, but to a lesser degree (Nigam et al., 1986; Soma et al., 1989); the net effect was interpreted to indicate the counteraction by Mg of factors that constrict the vasculature. Canine coronary arteries exposed to twice normal Mg levels did not alter NO-dependent relaxation, but directly inhibited spontaneous release of NO, and was thus considered important for expression of endothelial-dependent relaxation induced by acetylcholine and thrombin (Ku and Ann, 1991). Dietary deficiency in normal humans caused marked increase in TXB, which was reduced after Mg infusion

(Nadler et al., 1989). Physical stress of marathoners gave rise to an inverse relationship between serum Mg and TXB. The TXB fell slightly early in the race, but rose 9-fold by the end of the race, at which time serum Mg levels had fallen (Franz et al., 1985).

The vasoconstriction induced by ET-1 is Ca dependent, and can be blocked by Ca antagonists but not by nitrovasodilators or NO (Dinh-Xuan, 1989; Kiowski, 1991). ET-1 liberates Ca^{2+} , and stimulates Ca channels (Masaki et al., 1990), effects antagonized by Ca-channel blockers (Lovenberg and Miller, 1990). As in vascular muscle, Mg^{2+} plays a role in Ca^{2+} homeostasis in endothelial cells, probably via Na^{+} - Ca^{2+} exchange; such Mg^{2+} regulation participates in expression of endothelial-dependent relaxation (Zhang et al., 1990). Ca-channel blockage also inhibits ET-1 contraction of bronchial smooth muscle *in vitro* (Lerman et al., 1990). Since Mg is a physiologic Ca blocker (Iseri and French, 1984), the use of Mg in bronchial asthma might be mediated, not only through its anti-histamine-release effect (Hungerford and Karson, 1960) which is countered by excess Ca (Bertelsen and Johansen, 1991), but through its effect on ET-1 (Brunner et al., 1985; Mathew and Altura, 1988; Rolla et al., 1988). More direct data on the influence of Mg on the ET-1 effect has been derived from studies of Ca-channel currents in neurones (Nishimura et al., 1991). High-Mg containing solutions depressed the ET-induced current.

V. INTERRELATIONS AMONG CATECHOLAMINES, MAGNESIUM AND CALCIUM

Studies with catecholamine-secreting granules from adrenal medulla or nerve endings exposed to low-Mg/high-Ca ratios or high-Mg/low-Ca ratios have shown that low Mg increases catecholamine release and that high Mg decreases it, whereas Ca has reciprocal effects (Douglas and Rubin, 1963; 1964; Boullin, 1967; Kirpekar and Misu, 1967; Euler and Lishajko, 1973; Baker and Rink, 1975). The effect of verapamil, a Ca-channel blocker, on catecholamine release has been compared with that of Mg, a physiologic Ca-blocker. Lowering Mg levels has caused dose-dependent elevation of norepinephrine in cats. Reduction of Mg caused increased vasoconstriction of norepinephrine-contracted vein segments (Szabo et al., 1992), but norepinephrine-induced contractions were not affected in the mesenteric artery at low *ec* Mg (0.8 mM vs normal, 1.2 mM); high (1.6 and 2.0 mM) Mg had a modest inhibitory effect on the contractile responses (Szabo et al., 1991). Cerebral arterial contractions of the cat induced by norepinephrine *in vitro* were enhanced by low and inhibited by high Mg concentrations, the effect being attributed to both inhibition of Ca influx and binding of acetylcholine to an endothelial receptor (Farago et al., 1991).

Evidence that Mg could counteract Ca-induced catecholamine release from arterial nerves led to the first premise that low levels of Ca in blood might lead to low arterial tone, which in turn suggested that high Ca levels might increase blood pressure (Burn and Gibbons, 1964). The earliest clinical use of *iv* Mg was to control the hypertension of eclampsia (Lazard, 1925). Although thiazide diuretics largely replaced Mg for a time to manage pregnancy-induced hypertension, return to Mg was urged as the primary treatment, replacing all other modalities, because in addition to lowering high blood pressure of toxemic pregnancy, it increases uterine blood flow, depresses uterine hyperactivity and is associated with improved fetal salvage (Zuspan and Ward, 1965). It is noteworthy that the thiazide diuretics have long been known to increase Ca retention (Lamberg and Kuhlback, 1959; Duarte and Bland, 1965), while increasing Mg excretion (Smith et al., 1962; Wacker and Parisi, 1968; Unsigned Editorial, 1975; Dyckner and Wester, 1984; Leary et al., 1984). Contributory to the adverse effects of Mg inadequacy in pregnancy is the effect of high Ca/Mg ratio on intravascular coagulation - especially in the placenta, where endothelial damage participates in the pathogenesis of eclampsia, and in which Mg treatment increases PGI synthesis by endothelial cells (Watson et al., 1986; Briel et al., 1987; Seelig, 1993).

VI. MAGNESIUM/CALCIUM RATIOS IN COAGULATION

Many steps in the coagulation cascade, that are stimulated by Ca, are inhibited by Mg (Huntsman et al., 1960; Zahnert and Oloffs, 1960; Greville and Lehmann, 1944; Born and Cross, 1964; Hovig, 1964; Lorand and Konishi, 1964; Silver, 1965; Penglis and Michal

Table 1

Calcium and Magnesium Effects on Blood Coagulation

	Calcium	Magnesium
Factor VII activation	Dependent*	?
Factor X activation	Dependent**	?
Prothrombin → thrombin	Dependent**	Inhibited
Prothrombin time	Shortened	Lengthened
Prothrombin consumption	Increased	Decreased
Fibrinogen → fibrin	Increased	Decreased
Platelet adhesiveness	Increased	Decreased
Serotonin release (increases platelet clumping)	Increased	Decreased
Fibrinolysis	?	Increased
Fibrinolysis inhibition	?	Decreased

* + lipoprotein tissue factor. ** + phospholipid
Taken from Seelig (1993).

1969; Herrmann et al., 1970; Ardlie et al., 1970; Doni and Fantin, 1975) (Table 1) Practical application of the anticoagulant activity of Mg is suggested by the early work showing that Mg supplements prevented spontaneous myocardial infarction (MI) occurring in rats, dogs and cocks on Mg-deficiency inducing, nutritionally imbalanced atherogenic diets, that were rich in calcemic vitamin D (Sos, 1965; Rigo, 1971). In a more specific study, Mg deficiency was found to contribute to increased platelet aggregability that increased myocardial vulnerability to ischemic injury in Mg-deficient hamsters (Rishi et al. 1990). Additionally, Mg has prevented platelet aggregation on experimentally damaged endothelium, an activity that has been interpreted as applicable to prevention and treatment of ischemic heart disease (IHD) (Kurgan et al., 1980; Gertz et al., 1987).

Mechanisms by which a high Ca/Mg ratio increases platelet aggregation also entail PG and TXB. Dietary Mg deficiency in normal volunteers stimulated PGI and TXB synthesis and increased platelet aggregation that was corrected by Mg infusion (Nadler et al., 1989, 1991). Diabetics, who have low ionic Mg levels, and normal subjects on a low enough Mg die to cause hypomagnesemia had increased platelet reactivity that could be reduced either by Mg infusions or by oral Mg supplements at 400 mg/day (Nadler et al., 1992).

VII. NEUROMUSCULAR FUNCTIONS AFFECTED BY MAGNESIUM AND CALCIUM

A. Historical aspects

The first published account of the efficacy of Mg in management of a variety of nervous complaints, including anxiety, depression, hypochondria, anorexia, headache, and cramps, among other disturbances, was in a seventeenth century booklet (Grew, 1697). The functional similarity of Ca and Mg in muscle contraction (in vitro inhibition of rhythmic contraction of frog's gastrocnemius muscle) was an early subject of systematic investigation (Loeb, 1900). Not only Ca and Mg, but beryllium, barium, strontium, manganese, and cobalt suppressed spontaneous muscle contractions. Ca was soon thereafter shown, in rabbits, to antagonize inhibitory effects of Mg on irritability of contractile tissue and motor nerve endings (Meltzer and Auer, 1908). These early investigators emphasized the muscle relaxing effect of Mg in lower than toxic doses. Spontaneously occurring imbalances between Ca and Mg intakes that caused neuromuscular disturbances were first recognized in cattle (Seekles et al., 1930; Sjollem, 1932).

Only the aspect of the effect of Mg that relates to Ca is considered here (based principally on reviews by Chutkow (1971; 1980). Although hypocalcemia and hypomagnesemia each causes clinically manifest neuromuscular irritability, nerve physiology studies show that the mechanisms are not the same. Ca is chiefly involved in nerve axon membrane potential and stability. The effects of Ca or Mg depletion at this site are similar, but that of Ca far outweighs that of Mg. The moiety of *ec* Mg that is not bound participates principally in neuromuscular transmission at the myoneural junction where Ca and Mg are antagonistic. Mg impedes the entry of Ca into the nerve terminal, thereby reducing the release of acetylcholine. Mg deficiency has the opposite effect. Penetration of the nerve presynaptic membrane by Ca is low when the membrane potential (E_m) is at resting levels. Depolarization of the presynaptic membrane greatly increases Ca influx and release of acetylcholine. Mg blockage of neuromuscular transmission has long been known to be counteracted by Ca (Bryant et al., 1939). The effects of Mg on impulse transmission from nerve to muscle clarified its pharmacologic effects at the neuromuscular junction (Engbaek, 1952; del Castillo and Engbaek, 1954). At concentrations above physiologic, but below those that prevent nerve conduction, Mg activates cholinesterase, which destroys the neurotransmitter, and reduces the release of acetylcholine, effects which are counteracted by Ca.

C. Therapeutic aspects

Neuromuscular irritability, that can cause seizures and tetanic spasms, occurs with either hypomagnesemia or hypocalcemia, and responds to appropriate repletion. Since Ca-refractory hypocalcemia not infrequently results from Mg deficiency, which causes refractoriness of target organs to PTH or failure of PTH-release and decreases synthesis of the active metabolites of vitamin D (Fatemi et al., 1991), its appropriate treatment is Mg rather than Ca.

The latent tetany syndrome, accompanied by a variety of "psychosomatic" complaints, that develops despite normal Ca levels, has been clearly identified as a Mg-deficiency disorder (Durlach, 1960; 1988) (see Part Five, Chapter 1-B).

VIII. CARDIOVASCULAR FUNCTION

A. Historical aspects

The efficacy of *iv* Mg in arrhythmias caused by *iv* Ca was first demonstrated in cows being treated for grass tetany (Seekles et al., 1930). The potential clinical hazard of *iv* Ca was first shown in 1928 by Lloyd, who injected himself with CaCl_2 ; 50cc of a 1% solution produced no adverse effects, but after only 4cc of a 10% solution had been given, cardiac arrest ensued, with recovery on cessation of the injection.

The similarity of the effects of high-dose *iv* Ca to the therapeutic effect of digitalis, but with more rapid onset of effects, led to its being considered additive in cardiotherapy; it increased blood pressure and slowed the heart rate, but could cause bradycardia, heart block and arrhythmias (Lieberman, 1930). Therapy with combined digitalis and Ca was deemed safe in the 1930s (Berliner, 1936), but death of digitalized patients given *iv* Ca (Bowers and Mengle, 1936) led to reevaluation of this therapeutic approach (Golden and Brams, 1938). Conversely, the earliest human use of Mg was in the treatment of arrhythmias caused by digitalis toxicity (Zwillinger, 1935). Use of *iv* Ca salts to measure circulation time was replaced by Mg salts because of the risk of Ca injection, which had to be rapid for this test despite the generally accepted caution that Ca had to be injected slowly to minimize its toxicity (Berliner, 1936). In contrast, such use of *iv* Mg in a large series of patients was free of deleterious effects (Bernstein and Simkins, 1939).

Subsequent disagreement as to use of Mg for cardiac arrhythmias stemmed largely the ephemeral effect of the customary use of single doses (Enselberg et al., 1950), despite the evidence of its efficacy in antagonizing the increase by Ca of cardiac stimulus formation (Boyd and Scherf, 1943) without untoward effects. The inward shift of Ca stimulated by catecholamines is important in cardiac contractility, but can be excessive in patients with IHD, in which case the chronotropic responses to catecholamines (that concern rhythmicity)

predominate, and there is increased risk of arrhythmia and myocardial damage (Nayler, 1981). When there is Mg inadequacy, even in normal subjects, the chronotropic effect of catecholamines may cause arrhythmia and even sudden cardiac death.

There were only occasional publications on use of Mg in clinical arrhythmias and IHD (Zimhdal, 1946; Szekely, 1946; Szekely and Wynne, 1951; Malkiel-Shapiro et al., 1956; Malkiel-Shapiro, 1958; Parsons et al., 1959), until its importance was clarified in the 1970s, even without overt Mg deficiency (Iseri et al., 1975; Specter et al., 1975). Its use in digitalis toxicity and in thiazide-induced arrhythmias which relate to concomitant Ca excess became more popular (Dyckner and Wester, 1979; 1984; 1987; Leary et al., 1984; Reyes and Leary, 1984; Reyes, 1987). At the Fifth International Mg Symposium, in Japan, the importance of Mg in correcting the electrolyte disturbances associated with arrhythmias was reviewed (Iseri, 1989; Whang, 1989). That Mg treatment actually replenishes a deficiency was pointed out by Charbon (1989), who further commented that Mg and Ca act as antagonists with regard to cardiac arrhythmia. Direct evidence of the life-saving potential of post-infarct Mg infusions has been shown by controlled double-blind studies in which there was substantial reduction of post-MI arrhythmias and deaths (reviews: Rasmussen, 1988; 1989; Shechter, 1990; Teo et al., 1991).

IX. DISEASES WITH INTESTINAL OR RENAL LOSS OF MAGNESIUM OR CALCIUM

Clinical intestinal malabsorption can interfere with absorption of both Mg and Ca. Routine laboratory procedures usually detect hypocalcemia; more likely to be missed is hypomagnesemia, because Mg levels are not usually provided unless specifically requested. Thus, malabsorptive disorders, whether inflammatory or ulcerative bowel disease, malabsorption of fat (i.e. celiac disease, steatorrhea), or after intestinal resection or bypass, persistent diarrhea, and other forms may result in Mg deficiency that is severe before it is detected and treated (Hammarsten and Smith, 1957; Balint and Hirschowitz, 1961; Goldman et al., 1962; Heaton et al., 1964; Gerlach et al., 1970; Ladefoged et al., 1980; Nyhlin et al., 1982; Hessov, 1983; Selby et al., 1984; Galland, 1988; Sjögren, 1988). High intestinal fat content interferes with absorption, not only of Mg, but of Ca and Zn (Hessov et al., 1983). The specific genetic malabsorption of Mg invariably results in Mg deficiency, that is usually first identified by failure of hypocalcemia to respond to calcemic therapy (Paunier and Radde, 1965; Paunier et al., 1968; Skyberg et al., 1968; Friedman et al., 1967). Decreased Mg absorption has also been reported in renal failure, with progressive decrease of Mg absorption as renal failure progresses (Parlier et al., 1963; Mountokalakis et al., 1980).

Renal Mg wastage causes hypomagnesemia, again usually with secondary hypocalcemia; it can result from therapeutic drugs, disease (including alcohol abuse and diabetes mellitus) (Flink et al., 1957; Kalbfleisch et al., 1963; Mendelson et al., 1969; Medalle et al., 1976; Hui et al., 1985; Rude and Ryzen, 1986; Flink, 1986) from renal genetic defects, including Bartter's syndrome (Freeman and Pearson, 1966; Gitelman et al., 1966; Michelis et al., 1972; Runeberg et al., 1975; Rude et al., 1983; Rude and Ryzen, 1986; Dupond et al., 1989).

When hypocalcemia is diagnosed, and Mg deficiency is not suspected, treatment with Ca salts and/or with calcemic agents is the usual approach, but is one that intensifies the underlying Mg deficiency and that can result in soft tissue Ca deposition (Seelig, 1971; 1980; 1981; 1986; 1990; 1993; and Part Four, Chapter 5-A). Neuromuscular hyperirritability and increased vascular tonicity are examples of the overlap of manifestations of Ca and Mg deficiencies. The combination of hypomagnesemia with hypocalcemia has been recognized as contributory to human neonatal tetany, spasms and convulsions (Tsang and Steichen, 1975), as well as to comparable manifestations in adults with Mg deficiency from malabsorption or renal wastage. The symptoms respond better to Mg than to Ca treatment (Turner et al., 1977).

Disorders associated with hypercalcemia and hypercalciuria include conditions that increase intestinal absorption of Ca, as can result from sarcoidosis (Pak, 1979), vitamin D toxicity or hyperreactivity to vitamin D (Seelig, 1969). The hypercalcemia of

hyperparathyroidism and neoplastic osteolytic processes is derived from mobilization of Ca from the bone. In contrast, hypermagnesemia is an uncommon clinical problem; its neuromuscular, respiratory, and cardiac depressant effects can be temporarily controlled by Ca infusions (Rude and Singer, 1981). It can result from high Mg intake, as cathartics or antacids, almost exclusively by those with renal decompensation. Hypermagnesemia has been seen in neonatal infants before adequate renal function has developed (i.e. those born to eclamptic mothers who had received hypermagnesemia-inducing parenteral Mg treatment to control their convulsions and hypertension (Lipsitz, 1971) or very immature infants especially those whose hypocalcemia was treated by high-dose iv Mg (Tsang, 1972).

X. CONCLUDING COMMENTS

Whether deficiencies of Ca or Mg are caused by relative excess intake of one in the face of inadequate intake of the other, or whether caused by drugs or nutrients that enhance the absorption or cause loss of one over that of the other, they can have serious consequences - functional and structural.

Mg dietary intakes in the Occident are marginal or low; with some exceptions, the dietary intake of Ca is usually adequate. Occult Mg deficiency, and even frank hypomagnesemia (that is undetected) is a more common problem than is Ca deficiency. Hypermagnesemia is uncommon as compared with hypercalcemia. The current emphasis on Ca supplementation to bring intakes to as high as 2 g/day, which with the RDA for Mg being about 300 mg/day or less, constitutes a public health risk.

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Chapter 4: Interdependent Roles of Metal Ions

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