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Magnesium deficiency and the cardiovascular system

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Magnesium plays an important role in maintaining the structural and functional integrity of the cardiovascular system. Its influence on cardiac ion channels has immense clinical implications and is the subject of several incisive investigations. Magnesium deficiency may lead to a wide spectrum of vascular and cardiac complications. This article reviews evidence that magnesium deficiency promotes hypercoagulability of blood, atherogenesis, vasoconstriction, cardiac arrhythmias and cardiac muscle damage. Mechanisms underlying these effects are briefly discussed. Further, it is proposed that the myocardial lesions of chronic magnesium deficiency may result from recurrent episodes of mild ischaemia and reperfusion and consequent free-radical generation.

ONE of the most abundant cations within mammalian cells, magnesium (Mg) is an important metabolic cofactor, particularly in transphosphorylation reactions. It has been known for a long time that more than 300 enzymatic reactions require Mg and that the biosynthetic repertoire of the cell is critically dependent on it. Mg also functions as a transmembrane and intracellular modulator of other ions. However, it was only recently that the regulatory role of the element has been recognized in the wake of the discovery that intracellular free Mg, $[Mg^{2+}]_i$, is in the submillimolar range and that several intracellular systems have K_m values for Mg within this range[1]. This opens the possibility that $[Mg^{2+}]_i$ may vary physiologically and act as a physiological modulator.

The emergence of Mg as a premier cardiovascular cation follows important observations on the cardiovascular consequences of Mg deficiency which is no longer considered a mere laboratory phenomenon. Understandably, there is increasing interest in the cellular and molecular actions of Mg and their relevance to clinically recognized cardiovascular events in humans. This review discusses briefly the link between Mg deficiency and abnormalities in cardiovascular function and examines the underlying mechanisms.

Incidence of magnesium deficiency

A major problem in assessing the role of Mg status in the aetiology of diseases is the inadequacy of the indicators of Mg status[2]. As only 1% of the total body Mg is in the extracellular fluid, the total serum Mg may not reflect body stores. It is now amply clear that Mg depletion in tissues can exist despite normal serum Mg levels[2]. Cardiac disorders have been described[2] in cases with normal serum Mg and lower tissue Mg. Low serum Mg and normal cellular total Mg content without clinical signs of Mg deficiency have also been reported. Further, the reported normal values for serum Mg fall within a rather broad range, making it hard to know what constitutes an acceptable level. Since <10% of intracellular free Mg is freely exchangeable or ionizable Mg^{2+}, it is suggested that this fraction could be a better determinant of potential consequences of Mg deficiency than either serum Mg or total cellular Mg^{2+}. Nuclear magnetic resonance promises a reliable correlation between $[Mg]_i$ and diagnostic indices of Mg deficiency, but is not easily accessible[2].

Be that as it may, a series of clinical reports in the early 1960s helped focus attention on the occurrence of

hypomagnesemia[3]. Congenital primary hypomagnesemia, familial hypomagnesemia and hypomagnesemia associated with hypocalcemia, hypokalemia and hyponatremia have been reported[3]. Studies carried out in the US show that the overall incidence of hypomagnesemia in hospitalized patients ranges from 7 to 52%[4]. Increased intake of calcium, phosphate, fat, sugar or vitamin D enhances the requirement for Mg while diarrhoea and certain types of drugs, like the diuretics, induce Mg loss[5]. Reduced dietary intake of Mg through inadequate consumption of leafy vegetables, legumes, cereals and dairy products results in Mg deficiency[5]. Water is a source of Mg and the correlation between consumption of soft water (low Mg) and incidence of ischaemic heart disease should be a matter of concern to those living in soft-water regions.

Cardiovascular disturbances in magnesium deficiency

The major cardiovascular consequences of Mg deficiency are: (1) hypercoagulability of blood; (2) increased severity of atherosclerosis; (3) higher coronary artery tone or tendency for spasm; (4) greater myocardial vulnerability to arrhythmia; and (5) pathogenesis of the cardiomyopathy of Mg deficiency. While this article touches upon these aspects, the reader is referred to excellent and more comprehensive reviews on the subject[1,4–8].

Magnesium and haemostasis

The beneficial action of Mg in acute coronary syndromes relates to its effects on clotting. Several studies show that oral or intravenous Mg prolongs the clotting time of whole blood and delays the time to peak thrombin generation[5]. Another important observation is the inhibitory effect of supranormal concentrations of Mg on platelet aggregation[9]. Pretreatment of dogs with Mg was found to decrease platelet adhesion at the site of partial coronary occlusion by suture ligation[10]. Nadler *et al.*[11] observed that Mg infusion reduces thromboxane B_2 synthesis and thrombin-induced platelet aggregation in humans. In another experiment, application of a solution of $MgSO_4$ to injured rabbit artery or intravenous infusion of $MgCl_2$ was found to suppress thrombin formation[12]. These and several other experiments carried out in different laboratories have confirmed the anticoagulant properties of Mg.

Magnesium and atherosclerosis

Recent investigations have revealed the nexus between Mg deficiency and perturbations in plasma lipids that would favour atherogenesis. Elevated levels of cholesterol, triglycerides and LDL and diminished levels of HDL have been observed in Mg-deficient rats[13,14]. Rasmussen *et al.*[15] found, in a study on humans, a 27% reduction in triglycerides and VLDL after three months of Mg therapy. This study also showed a significant reduction in apoprotein B, no change in total cholesterol and an elevation in plasma HDL. A significant improvement in the HDL:LDL + VLDL ratio with $MgCl_2$ supplementation was observed by Davis *et al.*[16] in a 4-month clinical trial. Studies on high-risk individuals by Singh[17] showed a 29% incidence of cardiovascular complications and 11% death rate in individuals on Mg-rich diet as against corresponding figures of 60% and 18% in individuals on control diet. As expected, the group on Mg-rich diet had higher serum K and Mg levels and slightly lower total cholesterol levels. It appears, therefore, that Mg status influences atherogenesis.

Magnesium and vascular tone, vasospasm and hypertension

Over the last few years, many investigators have shown that administration of Mg produces dose-dependent reduction in arterial blood pressure, reduction in vascular resistance across different organ beds (such as heart, kidney and brain) and increased vascular perfusion (across coronary and renal vasculature)[7]. Elegant experiments have demonstrated the effect of Mg on vasoconstriction. For instance, when $[Mg]_o$ is lowered or withdrawn from the blood (or perfusate), arterioles and venules in the peripheral and cerebral microvasculature undergo marked vasoconstriction. Mg seems to affect arterial tone in many vascular beds and reduction in $[Mg]_o$ results in elevation of tension development in different mammalian arteries like the coronary artery, aorta or the cerebral arteries. Interestingly, increase in mechanical activity upon reduction of $[Mg]_o$ is greatly diminished and rapidly disappears when $[Ca]_o$ is lowered or chelated, suggesting that Ca influx is necessary for such contractile responses. It becomes evident from these observations that Mg is an important regulator of coronary, cerebral and peripheral vascular tone, which are related to unstable angina pectoris, coronary vasospasm, stroke and hypertension. Recent studies on the effect of Mg on release of endothelin- and endothelium-derived relaxing factor, two potent vasoactive agents, show that Mg deficiency may influence initiation of coronary vasospasm through these agents. Inverse relationship between concentration of Mg in drinking water and incidence of hypertension or ischaemic heart disease is documented. Mg deficiency in patients with variant angina, suppression of angina upon intravenous administration of $MgSO_4$ in patients with coronary artery spasm, association between ischaemic heart disease and low myocardial Mg, and perturbation in Mg balance in acute myocardial infarction amply illustrate the vascular

effects of the element[5,8]. Whether Mg acts as a natural antihypertensive and Mg supplementation confers protection against vasospasm warrants further scrutiny.

Magnesium and cardiac arrhythmias

Early afterdepolarizations are oscillations in membrane potential that cause repetitive depolarizations, referred to as triggered activity, which is also the term that describes cardiac arrhythmias. Mechanisms underlying early afterdepolarizations are yet to be delineated clearly but are believed to be related to a block of the inward rectifying current[18,19]. Davidenko *et al.*[20] and Kaseda *et al.*[21] have demonstrated inhibitory effect of Mg on early afterdepolarization produced by various agents. Mg was also shown to suppress early afterdepolarization and tachyarrhythmias induced by cesium in dogs[22]. The observed effect was attributed to an increase in inward rectifying K^+ current. Further, it was also suggested that suppression of triggered activity may be related to a stabilizing or surface charge effect that enhances the threshold current requirement for activation of triggered response[20]. Whatever the mechanism, ventricular and atrial arrhythmias are related to Mg deficiency in many clinical settings and successful treatment of arrhythmias with parenteral Mg is reported in many cases.

A look at the regulation of ion channels by Mg would explain the aforementioned effects of the element on vascular tone and cardiac arrhythmias.

Magnesium and cardiac ion channels

Magnesium and Ca^{2+} channels. Underlying many of the cardiovascular effects of Mg is the modulation of Ca^{2+} flux by both $[Mg^{2+}]_o$ and $[Mg^{2+}]_i$. In fact, Mg is believed to be a naturally occurring Ca^{2+} antagonist[23]. The systems that regulate Ca^{2+} flux and maintain Ca^{2+} levels within normal physiological range are sarcolemmal Ca^{2+}-ATPase, sarcolemmal Na–Ca exchange, sarcoplasmic reticular-Ca-ATPase and mitochondria. It appears that Mg^{2+} does not regulate the sarcolemmal Ca-ATPase as its affinity for Mg^{2+} is about 53 μM in presence of 1 mM ATP and physiological $[Mg^{2+}]_i$ is about 10 times this value so that fluctuations in $[Mg^{2+}]_i$ are unlikely to affect it[1]. Further, unlike divalent and trivalent cations which inhibit Ca uptake via the Na–Ca exchange mechanism in cardiac sarcolemmal vesicles, Mg^{2+} seems to have little effect on influx and efflux through the exchange[24].

However, Ca handling by the sarcoplasmic reticulum is regulated by Mg^{2+}. The dependence of Ca-ATPase activity on Mg^{2+} in the range 0.1–1 mM is extremely steep. The ability of sarcoplasmic reticulum to accumulate Ca is optimal when $[Mg]_i$ is 1 mM, which is well within the physiological range. $[Mg^{2+}]_i$ above or below this range is apparently inhibitory. Considering that Ca^{2+} flux across the sarcoplasmic reticulum is a primary mechanism of regulating $[Ca]_i$ in mammalian cardiac cells, it has been proposed that minor fluctuations in $[Mg^{2+}]_i$ may have major effects on $[Ca^{2+}]_i$ and hence cardiac activity[1].

Mitochondria from cardiac muscle sequester Ca in a respiration-dependent manner[25]. As this is inhibited by Mg with an approximate K_i of 3.1 mM, the ability of mitochondria to buffer $[Ca^{2+}]_i$ is believed to be influenced significantly by $[Mg^{2+}]_i$ in the physiological range.

Magnesium and K^+ channels. Six distinct cardiac K^+ channels have hitherto been identified by single-channel current recordings. Many of these channels exhibit inward rectification, allowing K^+ to pass more readily in the inward direction than in the outward direction[26]. Available evidence suggests that Mg^{2+} blocks the outward movement of K^+ through these channels. It is found that when the solution bathing the cytoplasmic side of the membrane contains Mg^{2+}, these channels rectify inwardly, as they do in the cell. However, when Mg^{2+} is removed, the channel no longer rectifies but carries current equally in both the directions[27–30]. Thus, it appears that internal Mg^{2+} acts as a naturally occurring K^+ channel blocker which plugs the open channel in a voltage-dependent manner from the inner surface of the sarcolemma, preventing outward movement of K^+. In other words, Mg^{2+} plays a role in the rectification of this channel and hence in depolarization and repolarization.

Mg influences rectification of the ATP-sensitive K^+ channel in much the same way. Interestingly, during hypoxia or ischaemia, a rise in $[Mg^{2+}]_i$ following ATP depletion promotes inward rectification of this channel[28]. Further, the inward rectification of acetycholine-activated K^+ channel is also regulated by $[Mg^{2+}]_i$ through voltage-dependent block of outward rectification[29]. It is pertinent to point out that these channels are activated by stimulation of muscarinic cholinergic receptors via a G-protein whose activation requires $[Mg^{2+}]$[31,32]. Thus, activation of this channel by acetylcholine or GTP requires Mg^{2+}. Some cardiac cells have Ca^{2+}-activated channels that are involved in repolarization[33]. It is suggested that Mg^{2+} increases the affinity for Ca^{2+} of a similar Ca^{2+}-activated channel in salivary gland acinar cells[34]. It is unclear if $[Mg^{2+}]_i$ regulates these channels the same way in cardiac muscle. $[Mg^{2+}]_i$ also appears to influence the delayed rectifier K^+ channel that is responsible for membrane repolarization after an action potential.

It is noteworthy that Mg is used in cardioplegic solutions (used in cardiac surgery to 'paralyse' the cardiac muscle) for its protective effect, which is related to Mg^{2+}–Ca^{2+} and Mg^{2+}–K^+ interactions at the sarcolemma. It is found that when high concentrations of Mg are employed in cardioplegic solutions, tissue enzymes and

mitochondrial oxidative phosphorylation are preserved[7]. Further, the effects on vessels discussed above ensure better perfusion. To summarize, the regulatory effects of Mg on the cardiovascular system relate to its influence on transmembrane flux of other ions, mainly Ca^{2+} and K^+, which has a bearing on the generation of cardiac action potential.

Magnesium deficiency and cardiac pathology

Among the important cardiovascular consequences of Mg deficiency is the increased vulnerability of the myocardium to necrosis. Myocardial lesions of Mg deficiency, which are in the nature of a cardiomyopathy, have been studied in animal models. In humans, it is most likely that the effects are masked by other deficiencies. Typically, the morphologic finding is one of focal necrosis and calcification progressing to fibrosis[6]. However, these changes are not specific and are seen in other conditions such as alcoholic cardiomyopathy. Heggtveit *et al.*[35,36] found an array of myocardial changes as early as two weeks after rats were placed on a Mg-free diet. Focal myocardial necrosis, manifesting subendocardially, enlarge, develop areas of calcification and become more numerous as deficiency advances. Vascular dilatation and hyperaemia are prominent in the early lesions of Mg deficiency. As it progresses, fragmentation, vacuolization and eventual myocyte loss are noticed along with progressive increase in macrophages, fibroblasts and collagen. Electron microscopy reveals prominent early mitochondrial swelling and loss of internal fine structure. As deficiency becomes more severe, mitochondria calcify and coalesce to form mineralized masses within the sarcoplasm of degenerating myocytes.

Theories on pathogenesis of the cardiomyopathy of Mg deficiency

Calcium overload hypothesis. An attractive theory to explain the pathogenesis of Mg deficiency cardiomyopathy has been put forward by Heggtveit[35], who stresses the role of Ca overload in the causation of myocardial necrosis. The earliest observed change in the Mg-deficient animal is a dip in serum Mg and elevation in myocardial Na. It is likely that a reduction in Mg-dependent Na, K-ATPase activity[37–39] causes Na^+ accumulation in the myocytes, which would also explain the electrical instability observed in the heart in Mg deficiency. Elevation of myocyte Na^+ would result in reversal of the Na–Ca exchange and a rise in intracellular Ca^{2+} (ref. 40). That the increased myocardial Ca level is due to the Na–Ca exchange is consistent with the observed lag in the increase of myocardial Ca level behind increase in the Na level[41]. Further, Mg is also Nature's Ca blocker, so that its deficiency causes Ca rise in the cell. Thus, the 'Ca overload' hypothesis emphasizes the role of elevated myocardial Ca in the development of Mg deficiency cardiomyopathy. Although Bloom[6] has noted that development of histological lesions parallels elevation of myocardial Ca and does not precede it, it is not quite clear whether Ca accumulation in the myocardium in Mg deficiency precedes necrosis or is secondary to it. While Ca rise could cause injury to the myocardium, it is conceivable that even prior to Ca loading, damage gets initiated through other mechanisms.

Free radical injury. Weglicki *et al.*[42–47] have pursued the hypothesis that O_2-derived free-radical production participates in the development of the cardiomyopathy of Mg deficiency. They have shown that Mg deficiency produces a generalized proinflammatory state marked by high circulating levels of inflammatory cytokines such as IL-1, IL-6 and TNF-α released by macrophages. These factors have been detected in the cardiac lesions of Mg deficiency. In experiments on rats, they demonstrated elevation of cytokine levels from day 12 in animals on the Mg-deficient diet, reaching a peak by day 21. Further, elevation of circulating levels of the neuropeptide, substance P, occurs at day 5. Substance P is known to produce several mediators of inflammation and both substance P and TNF-α trigger free-radical production. Increase in thiobarbituric acid reactive substances and protective effect of vitamin E during Mg deficiency further support the theory that Mg deficiency does promote free-radical generation. Further, a recent report from the same laboratory shows that substance P blockade by CP 96954 reduces accumulation of substance P and TNF-α in the cardiac lesions and attenuates rise in thiobarbituric acid reactive substances and reduction in glutathione associated with Mg deficiency. A neuropeptide/TNF-α/free-radical-triggered mechanism that may be the major pathway of systemic oxidative injury inducing cardiomyopathic lesions during Mg deficiency seems attractive indeed.

An integrated view. In the light of observations cited above, this author proposes that pathogenesis of the cardiomyopathy of chronic Mg deficiency involves early changes in the cardiac vasculature which may precede and promote changes in the myocardium. This is not to imply that other changes, such as impairment of the biosynthetic repertoire of the cell[48], do not contribute to the pathogenesis of the cardiomyopathy of Mg deficiency. Considering that myocardial Mg is well-preserved, such changes are not likely to represent early pathogenetic events. A tentative model (discussed below) merits attention.

Myocardial Mg levels do not generally decrease except in extraordinary conditions, as after ischaemia or upon administration of certain types of drugs. (In fact, even in experimental animals, a Mg-depleted diet fails to reduce significantly myocardial Mg over several

days.) On the contrary, hypomagnesemia, defined as decreased or suboptimal serum levels of Mg, can be more common in a population. It is, therefore, possible that the cardiac vasculature rather than the myocardium would be the site of early lesion in Mg deficiency. Considering the proven link between Mg deficiency and vasospasm, it is tempting to propose that chronic Mg deficiency, with occasional bouts of acute deficiency, may induce, through effects on vascular smooth muscle, episodes of mild ischaemia and reperfusion in the vasculature, which, as is well-known, would promote free-radical generation and eventual damage to the cardiac muscle. That the early myocardial lesions in Mg-deficient animals are localized around blood vessels is consistent with such a proposition. Cardiac fibrosis associated with the late stages of Mg deficiency is possibly reparative in nature and follows free-radical injury to the muscle. Interestingly, Kramer *et al.*[47] have recently observed that Mg deficiency potentiates free-radical generation associated with postischaemic injury to rat hearts; vitamin E was found to afford protection. The temporal sequence of ischaemic change and free-radical production in Mg deficiency *per se* needs to be elucidated.

Conclusion

Mg deficiency is clearly a risk factor for a spectrum of cardiovascular diseases. Importantly, subclinical Mg deficiency, whose incidence is possibly higher than one would expect, is a silent operator that can gradually impair the structural and functional integrity of the cardiovascular system. The questions that confront the investigator interested in Mg deficiency are the following:

1. What constitutes Mg deficiency?
2. What, if at all, is the prevalence of subclinical Mg deficiency in a population?
3. Is Mg supplementation desirable? If so, to what extent?
4. What are the molecular mechanisms underlying vascular changes and cardiac muscle damage and fibrosis associated with Mg deficiency?

Investigations along these lines would necessarily have to transcend conventional barriers between biochemistry, epidemiology, nutrition and clinical medicine and target the *terra incognita* of a new synthesis. A joint venture shall not be in vain.

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RESEARCH ARTICLES

Model calculations of competing climatic effects of SO_2 and CO_2 in fossil fuel combustion

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Fossil fuel combustion has two competing effects on the climate system, a warming due to the emission of CO_2 and other trace gases and a cooling due to sulphate particles formed from the SO_2 emission. A detailed parameterization of the relationship between fossil fuel burning and the SO_2 effect on backscattering and cloud albedo is implemented in a one-dimensional radiative–convective model for assessing the climatic impact. The results show that at present the cooling induced by the combined effect of SO_2 completely counteracts the CO_2 greenhouse warming. The model predicts that by the year 2060 the SO_2-induced cooling reduces warming due to CO_2 by 66% in the IPCC scenario BaU and by 27% in the IPCC scenario D. Attempts to slow-pace the fossil fuel burning will decrease the SO_2 concentration, which could further increase global warming.

WHEN fossil fuel is burned, both carbon dioxide and sulphur dioxide are added to the atmosphere. Carbon dioxide being a greenhouse gas has a warming effect on the climate system. The radiative effect of CO_2 is relatively easy to assess based on its infrared absorption and emission properties.

In the atmosphere, sulphur dioxide goes on to oxidize with compounds in the troposphere to produce aerosol particles. These hygroscopic submicron particles also affect our climate but in a different way. These particles scatter solar radiation back to space, causing a direct cooling – this is called the direct effect. These particles also increase the concentration of cloud condensation nuclei (CCN). An increase in the CCN concentration can cause an increase in the cloud droplet concentration, which will cause an increase in the total reflective surface area within the cloud, thus leading to an increase in the cloud albedo. This is called the indirect effect. Major difficulties in the study of climatic effect due to SO_2 emission result from the fact that the atmospheric sulphuric compounds have a short lifetime, a nonhomogeneous distribution of sources and a variable vertical distribution of concentration.

The increase and the predicted radiative forcing resulting from the four Intergovernmental Panel for Climate Change (IPCC) greenhouse gases emission scenarios were known to us. The Business-as-Usual (BaU) scenario represents a continued increase in the consumption rate of fossil fuel at the present pace. Scenarios B and C represent a lower rate of increase. Scenario D represents levelling off of the consumption rate close to the 1990 consumption rate and a decrease after the year 2010. Spatially specific projections of future climate change assumed CO_2 to be the only forcing agent in fossil fuel burning, aerosols having been ignored[1,2]. This means that projections may well be grossly in error over much of the world[3].

Charlson *et al.*[4] suggested that the direct SO_2-induced forcing is comparable but opposite to the anthropogenic CO_2-induced forcing. Recently Kiehl and Briegleb[5] and Taylor and Penner[6] calculated the direct radiative forcing due to sulphate aerosols. The indirect forcing was recently calculated by Jones *et al.*[7] At the present emission level, the SO_2-induced cooling has the potential of at least partially offsetting the CO_2-induced warming[8].

In this paper, we present a detailed analysis of the climatic effects of CO_2 and SO_2 using a one-dimensional radiative–convective model. Here we present an analysis of the relationship between fossil fuel burning, CO_2 and SO_2 emission, the concentration of anthropogenic CCN, reflected solar radiation and cloud albedo, along with a simulation of the combined SO_2 and CO_2 climatic effect.