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Genotoxic Effects of Magnesium Deficiency in the Cardiovascular System and their Relationships to Cardiovascular Diseases and Atherogenesis

Burton M Altura[1-5,*], **Nilank C Shah**[1,5], **Gatha J Shah**[1] **and Bella T Altura**[1,3,5]

[1]*Department of Physiology and Pharmacology, The School of Graduate Studies in Molecular and Cellular Science, State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[2]*Department of Medicine, The School of Graduate Studies in Molecular and Cellular Science, State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[3]*Center for Cardiovascular and Muscle Research, The School of Graduate Studies in Molecular and Cellular Science, State University of New York Downstate Medical Center, Brooklyn, New York, USA*

[4]*Bio-Defense Systems, Inc, Rockville Centre, New York, USA*

[5]*Oceana Biomedica, Estero, Florida, USA*

[*]**Corresponding author:** Altura BM, Department of Physiology and Pharmacology, State University of New Downstate Medical Center, Brooklyn, New York, USA; Tel: 718-270-2194; E-mail: baltura@downstate.edu

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Abstract

The authors present evidence for a novel, new hypothesis whereby magnesium deficiency (MgD) acts as a genotoxic agent which probably causes numerous, hertofore, unrecognized consequences, even over a short-term, on the physiological, molecular and biochemical machinery of cardiovascular tissues and cells. The end result of these genotoxic effects of MgD probably plays important roles in the etiology and generation of diverse cardiovascular diseases, atherosclerosis, inflammation, and strokes via alterations in the epigenome of cardiovascular tissues and cells. The importance of adequate water-borne and dietary levels of Mg is emphasized.

Keywords: Hypertension; Inflammation; Sphingolipids; Ceramide; Epigenetics

Introduction

Over the past two decades, a considerable amount of research has taken place around the globe suggesting that a variety of chemicals and mutagens can produce genotoxic effects in multiple tissues and cells [1,2]. Genotoxicity conotes in genetics a destructive effect(s) on a cell's genetic material (i.e., DNA, RNA) thus potentially altering cell integrity, functions, and phenotype [1].

Genotoxins are, thus, mutagens. Some of these well-known genotoxins include radiation of different types and chemicals known to damage DNA. The end result of genotoxins result in modification of gene expression. Although numerous advances are being made about genotoxins, very little is known about the potential mechanisms involved in how genotoxins induce lesions in DNA and how these agents could result in chromosomal abberations.

Recently, we have provided putative evidence that magnesium (Mg) - deficient environments can act like genotoxins on cardiovascular tissues and cells [3,4]. We provide, below, background, evidence, and our reasons for believing that magnesium deficiency(MgD) can result in genotoxicity in cardiovascular tissues and cells which probably play major roles in etiology of cardiac diseases, atherogenesis, inflammation, and stroke heretofore unexplained.

Disturbances in Diets and Magnesium Deficiency Linked to Cardiac Diseases, Atherogenesis, Inflammation, and Stroke

Disturbances in diets are known to promote lipid deposition and accelerate the growth and transformation of smooth muscle and endothelial cells in the vascular walls of blood vessels and promote vascular and cardiac dysfunctions of several types; e.g., atherosclerosis, heart rhythm disturbances, decreases in cardiac ejection of blood, decreased force of ventricular and atrial contractility, decreases in arterial blood pressure, diminished venous return to the heart, cardiac tamponade, hypertension, strokes, sudden-cardiac death, myocardial infarctions, etc. [5-7]. A number of epidemiologic studies in North America and Europe have shown that people consuming Western-type diets are low in magnesium(Mg) content (i.e., 30-65% of the RDA for Mg) [7-11]. Most of these diets in the U.S.A. show that 60-80% of Americans are consuming 185-235 mg/day of Mg [6,10]. In 1900, in contrast, Americans were consuming 450-550 mg/day of Mg [6,8]. Low Mg content of drinking water, found in areas of soft-water and Mg-poor soil, is associated with high incidences of atherosclerosis, ischemic heart disease(IHD), coronary vasospasm, hypertension, and sudden-cardiac death(SCD)[6,8,12-17]. Both animal and human studies have demonstrated an inverse relationship between dietary intake of Mg and atherosclerosis [5,6,8,18-21]. The myocardial level of Mg has consistently been observed to be lower in subjects dying from IHD and SCD in soft-water areas than those in hard-water areas[5,6,8,12,13,15,18,22]. Mg plays essential roles in more than 500 enzymatic reactions in the body [23] and is required for all energy-generating reactions and oxidative phosphorylation [23,24].

More than 45 years ago, two of us demonstrated that Mg^{2+} behaves as a natural calcium channel blocker in both cardiac and vascular smooth muscle (VSM) cells [8,12,22,24-29]. We also showed in experimental animals that Mg behaves as a natural statin in that it can lower blood cholesterol and triglyceride levels [6,8,18,19,30] as well as act as a powerful vasodilator in the microcirculation and as a cardiac muscle relaxant [8,18,26,27,31-35]. Hypermagnesemic diets have been shown to ameliorate hypertension and atherogenesis [6,8,12,18,24,30,36-40]. Using sensitive and newly designed specific Mg^{2+} ion selective electrodes, our laboratories demonstrated that patients with hypertension, IHD, cardiac failure, strokes, diabetes mellitus types 1 and 2, pregnant women with gestational diabetes, renal-induced vascular changes (associated with elevated serum cholesterol), preeclampsia, hemorrhage, sickle cell anemia in children (and adults), and atherosclerosis exhibit significant reductions in serum/plasma/whole blood levels of ionized, but not total blood levels of Mg [6,8,18,40-62]. In addition, our laboratories have also shown that dietary deficiency in rabbits and rats causes vascular remodeling concomitant with atherogenesis (i.e., arteriolar wall hypertrophy and alterations in the matrices of the vascular walls) and hypertension [6,8,18,19,63-65]. These results could be considered the end result of genotoxic effects. Some of these results have very recently been observed to result in an acceleration of the aging process [66,67]. We believe these latter (genotoxic?) actions of MgD are also potentially the end result of low environmental levels of Mg in body fluids and dietary composition. Many of the pathophysiological and pathological molecular-biochemical alterations typically observed in tissues and cells in the aging process have been noted in MgD tissues and cells of the cardiovascular system by our group and some other investigators [6,8,12,18-21,24,30,36,63,65,67-78].

Magnesium Deficiency Activates NF-kB and Proto-Oncogenes, Increases Ca^{2+} Uptake/Release, Releases Mitochondrial Cytochrome C, Releases Myocardial Enzymes, as Well as Produce Reactive Oxygen Species, Reactive Nitrogen Species and Nitric Oxide: Relationship to Oxidized LDL, Apoptosis, Ceramide, Cytokines, and Pathogenesis of Atherosclerosis and Hypertension

Studies from our laboratories [8,37,69,79,80] and others [71,72,75] have demonstrated that genotoxic reactants such as reactive oxygen species (ROS), reactive nitrogen species and enzymes that generate nitric oxide(e.g., eNOS and iNOS) are generated in MgD states. All of these reactants along with movement of Ca^{2+} into the vascular smooth muscle (and endothelial) cells (as a consequence of MgD) [6,8,22,24-30,37,65,68,73,81,82] help to oxidize low density lipoprotein (LDL) in the blood and vascular walls to promote atherogenesis. The oxidized LDL (oxLDL) plays an important role in the pathogenesis of atherogenesis, to a large extent, through the elevated Ca^{2+} ion concentrations which contribute to blocking apoptosis of the macrophages(normally needed to cleanse the blood of debris and elevated lipids), thus, promoting uptake of oxLDL which then help to transform normal contractile VSM cells to non-contractile new VSM cell phenotypes which act to produce and synthesize a variety of chemicals needed for the atherogenic process. Atherosclerosis is a complicated inflammatory disorder that involves activation, proliferation, changes in cell phenotypes (e.g., contractile VSM cells to non-contractile synthetic cell machines) and survival of macrophages [7,83]. In addition, for atherogenesis and hypertension to develop, pathways for activation of NF-kB and proto-oncogenes must perforce take place. MgD results in all of the latter in intact and in situ VSM and myocardial cells, at least in experimental animals [3,4,11,67,70,73,79,81,82].

The pathophysiology of hypertensive vascular disease involves vascular remodeling via the proliferation and migration of VSM cells [7,84]. Low $[Mg^{2+}]_0$ environments have been shown by our group [6,8,18,19,65,73] and others [66,75] to promote proliferation and migration of VSM cells. Moreover, our laboratories have demonstrated that vascular remodeling and inflammation, at the microcirculatory level, is seen in rabbits and rats whom are given diets low in Mg [6,8,11,18,19,37,63-65] which are similar to the low dietary levels of people now residing in North America and Europe. These pathological changes clearly are a consequence of the genotoxic effects of MgD. In cultured VSM and human endothelial cells, low Mg^{2+} results in the generation and release of cytokines, chemokines, and ceramides that are needed to mediate inflammatory events required for the initiation of atherogenesis [3,4,6,8,11,18,67,68,7073,74,79,81]. These events were demonstrated to involve activation of NF-kB via ROS, NOS, and nitric oxide synthase [6,8,11,67,69,70,73,79-82]. As we predicted, inhibition of cytokine release, inhibition of telomerase downregulation, inhibition of ceramide generation ,inhibition of myocardial enzyme release(i.e., lactic acid dehydrogenase, creatine kinase, troponon T), inhibition of NF-kB activation, or inhibition of activation of proto-oncogenes, in cultured VSM cells with excess Mg, were found to prevent or ameliorate the toxic vascular and cardiac effects of MgD [3,4,6,11,67,69,70,73,74,79,81].

Magnesium Deficiency Results in Oxidation and Fragmentation of DNA, Downregulation of Telomerase, And Increased Levels of Ceramide and P53: Relation to Cellular Mutations and Epigenetics

Two years ago, our laboratories demonstrated, for the first time, that 21 days of low dietary Mg intake in living rats, results in a downregulation of telomerase in cardiac and VSM muscle [67]. These exciting results appeared to be closely related to fragmentation and oxidation of DNA, increased cellular levels of ceramide and increased cellular levels of the tumor suppressor gene, p53 [3,67,70,74,79]. Our studies pointed to a sizeable cross-talk among telomerase, neutral sphingomyelinase (N-SMase) and p53 in rat cardiac and peripheral vascular smooth muscle exposed to short-term MgD [3,67]. We suggested that our results would be compatible with the idea that even short-term MgD could cause alterations of the epigenome in diverse cell types leading to mutations of cardiac, vascular, and endothelial cells in aging and atherogenesis. Two years ago, we suggested ways in which this hypothesis can be tested [67]. Recently, Thakore et al. [2] (among others) have stated "site-specific alterations of the epigenomic landscape in eukaryotic cells are a powerful strategy for interrogating the mechanistic relationships among chromatin state, gene regulation, and cell phenotype".

Importance of Mg-supplemented Drinking Water and Beverages: Role of Adequate Mg Intake to Overcome and Prevent Genotoxic Effects of Mg Deficiency

Over the past two -plus decades, our laboratories have demonstrated, at least experimentally, that we can overcome all of the genotoxic cardiovascular actions(i.e., physiological, biochemical and

molecular) of Mg deficiency in rats, rabbits and mice by either supplementing drinking water with Mg or adding Mg to the diets fed to the animals [3,4,6,8,18,19,67,68,74,79,81]. Our results, so far, bolster the idea that water intake (e.g., from tap waters, well waters, bottled waters, beverages using tap/well/spring waters, or desalinated waters) in humans should contain at least 25-40 mg/liter/day of Mg^{2+} [85]. The latter inclusion in our diets should go a long-way towards the prevention of cardiovascular diseases and ameliorate the atherosclerotic and inflammatory aspects of the aging process of bodily tissues and cells in humans worldwide. Interestingly, on the basis of our work (and some others), the World Health Organization has taken our recommendations seriously, for the first time [86]. Lastly, this has led Israel to supplement its desalinated drinking water, in the Southern part of the country, with Mg^{2+} to determine the cardiovascular benefits of this approach over a 5-year period [86].

Conclusion

Herein we review and present evidence for a novel, new hypothesis on why MgD can act as a genotoxic agent and potentially cause numerous adverse effects, even over a short-term, on the physiological, molecular and biochemical machinery of cardiovascular tissues and cells. The end result of such genotoxic effects of MgD probably plays important roles in the etiology and generation of diverse cardiovascular diseases, atherosclerosis, inflammation, and strokes via alterations in the epigenome of these cardiovascular entities. The importance of adequate waterborne and dietary levels of Mg is emphasized.

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