Commentary

Why typos in DNA may help to fuel atherogenesis and inflammation prior to heart attacks, ischemic heart disease, and sudden-death ischemic heart disease: roles of unrecognized ionized hypomagnesemia and epigenetics

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Burton M Altura,[1–6] Nilank C Shah,[1,6] Gatha J Shah,[1,6] Bella T Altura[1,3–6]

[1]Department of Physiology and Pharmacology, State University of New York Downstate Medical Center, USA
[2]Department of Medicine, State University of New York Downstate Medical Center, USA
[3]Cardiovascular and Muscle Research, State University of New York Downstate Medical Center, USA
[4]The School of Graduate Studies in Molecular and Cellular Science, The State University of New York Downstate Medical Center, USA
[5]The Magnesium for Health Foundation, USA
[6]Bio-Defense Systems, Inc, Rockville Centre, USA

Correspondence: Dr Burton M Altura, Department of Physiology and Pharmacology, School of Graduate Studies in Molecular and Cellular Science, SUNY Downstate Medical Center, Brooklyn, New York, USA, Tel 718-270-2194, Fax 718-270-3103, Email burton.altua@downstate.edu

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Introduction

A considerable number of clinical and experimental studies have taken place around the globe suggesting that diverse chemicals and mutagens can produce genotoxic effects in multiple tissues and cells.[1,2] Genotoxicity denotes, in genetics, a destructive effect(s) on a cell's genetic material (i.e., DNA, RNA), thus potentially altering cell integrity functions, and phenotypes.

Genotoxins are, therefore, mutagens. Several of these well-known genotoxins include radiation of diverse types and chemicals known to damage DNA. The final result of genotoxins induce modifications of gene expression. Even though numerous advances are being made every day about genotoxins, little is known about the potential mechanisms involved in exactly how genotoxins induce lesions in DNA and how these toxic agents result in chromosomal aberrations.

We have provided putative evidence that magnesium (Mg) deficient environments can behave like genotoxins on cardiovascular tissues and cells.[3–5] We continue this line of thought, below, for believing Mg-deficient environments can result in inflammatory lesions which can result in atherogenesis, thus leading to heart attacks, ischemic heart disease (IHD), cardiac failure (CF), sudden-death ischemic heart disease (SDIHD), and strokes.

DNA typos and disease etiology

When any cell divides, its six billion letters of DNA are copied with each new copy going to each daughter cell. During this duplication process, it is now known that so-called "typos" inevitably occur, and a cell's DNA-proofreading mechanism (s) "usually catch and correct" these typos.[6] But, sometimes this "catch-up and correct mechanism" fails, and if this occurs in certain critical regions of the genome, this can shuttle a cell into a new form of growth and differentiation.[6] Using this hypothesis, a team led by Tomasetti, Liu and Vogelstein, in 2017, with mathematical analyses, suggested "typos in DNA "were found in 32 different cancer types. They attributed these "typos" either to a heredity environment or "random DNA copying errors. Tomasetti et al calculated that 66% of cancer mutations occur from DNA copying errors.[6] Most of the others occurred via environmental factors according to their calculations.

Mg deficiency results in alterations in cardiovascular tissue and cellular telomerases, DNA, micro-rnas, inflammatory lesions and atherogenesis

Interestingly, we have recently reported that rats'cardiovascular tissues and cells, extirpated from rats fed Mg deficient diets,demonstrate a down-regulation of telomerases, oxidation and fragmentation of DNA, lipid peroxidation, alteration of micro-RNAs, methylation of DNA, and alteration in histones.[7–12] Taken together, such modifications in DNA, RNA, and micro-RNAs could easily account for development of inflammatory lesions, atherogenesis, and arterial plaques seen in our experimental rats, rabbits and guinea-pigs.

Disturbances in diet and Mg intake linked to development of inflammatory lesions and atherogenesis

Dietary alterations are known to cause 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 diverse types, i.e., atherosclerosis, heart rhythm disturbances, decreased force of ventricular and atrial contractility, increases in arterial blood pressure, diminished venous return to the heart, cardiac tamponade, hypertension, strokes, SDIHD, myocardial infarctions, etc.[13–15]

Several epidemiologic studies in North America and Europe, and The UK have shown that people consuming Western -type diets are quite low in Mg intake (i.e., 30-65% of the RDA for Mg)[16–18] Most

of The North Americans are consuming only about 185-235 mg Mg/day.[16–18] In 1900, Most diets in the USA contained about 450-550 mg Mg/day. Low Mg content of drinking water, found in areas of soft-water and Mg-poor soil, is associated with high incidences of atherosclerosis, IHD, coronary vasospasm (i.e., Prinzmetal spasm), hypertension, and SDIHD.[17,19–26] Are these facts coincidences?

Both animal and human studies have demonstrated an inverse relationship between dietary intake of Mg and atherosclerosis.[3–5,17,19,22–31] The myocardial level of Mg has consistently been observed to be lower in subjects dying from IHD and SDIHD in soft-water areas than those in hard-water areas.[17,19–25,32] Mg plays critical roles in more that 500 enzymatic reactions in the body,[33] and is required for all energy-generating reactions and oxidative phosphorylation.[7,33,34]

Approximately, 50 years ago, two of us demonstrated that Mg^{2+} behaves as a Ca^{2+}channel blocker at vascular smooth muscle membranes;[35–39] later we showed that Mg^{2+} modulated Ca^{2+} currents in capillary endothelial membranes[40,41] and regulation of intracellular Ca^{2+}.[37–39] We also showed that Mg plays a role as a "natural statin" in the body, as it can lower blood levels of cholesterol and triglycerides[10,17,27] as well as a powerful vasodilator in the microcirculation,[42–45] and a cardiac relaxant.[7,46–49]

Hypermagnesemic diets have been shown to ameliorate hypertension and atherogenesis.[26,27,42,45,50,51] Using sensitive and newly-designed specific Mg^{2+}-electrodes, our laboratories have demonstrated that many patients with drug-resistant hypertension, IHD, early cardiac failure, atrial fibrillation, alcoholic heart disease, diabetes types 1 and 2, pregnant women with preeclampsia-eclampsia, renal-induced vascular damage(associated with elevated serum cholesterol), loss of blood volume, headaches, and atherosclerosis exhibit significant reductions in serum/plasma/whole blood ionized Mg as well as intracellular free Mg.[5,17,22,29,52–106] Moreover, our labs have shown that dietary Mg deficiency, in rats and rabbits, causes vascular remodeling concomitant with atherogenesis (i.e., arteriolar wall hypertrophy and alterations in the matrices of the vascular walls) along with elevations in systolic (SBP), diastolic and pulsepressure(PP).[22,52,75,78,91,96,100,105,106] These findings could be considered the end results of genotoxicity. We have very recently presented new clinical molecular/biochemical data and a rationale for why and how Mg deficiency in type 2 diabetes induces elevations in both SBP and PP, as well as high risks for IHD and SDIHD, particularly in men over the age of 60.[105,106]

Several of our experimental results, found in diabetic and drug-resistant hypertensive subjects, have recently been observed to end-up in an acceleration of the aging process.[100,105,106] We firmly believe these latter genotoxic-epigenetic actions of Mg deficiency are also potentially the end result of low environmental levels of Mg in bodily 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 aging cardiovascular tissues, in animals and patients, by our group and by several other groups.[107,108] But, what are the specific mechanisms linked to Mg deficiency?

Roles of proto-oncogenes, NF-kB, p53, DNA damage, PKC isozymes, and epigenesis

NF-kB and **proto-oncogenes**

Atherogenesis is a complicated inflammatory process that involves activation, proliferation, and alterations in phenotypes (i.e., contractile smooth muscle cells change to non-contractile, secreting synthetic machines).[13–15,109] with survival of diverse macrophages changing to monocytes which invade the endothelial cells in the arteriolar and arterial walls.[109] In addition, in this evolving atherosclerotic process, NF-kB and the proto-oncogenes c-fos and c-jun must be activated.[110–113] We have, indeed found in Mg deficient animals and humans that both NF-kB and the proto-oncogenes c-fos and c-jun are activated and expressed.[4,9,17,28,75,78,91,100,104,114] In consonant with these molecular alterations, low Mg environments have been found, in our Mg deficient rats and rabbits, to promote proliferation and migration of diverse cell types needed for generation of atherogenesis.[5,17,22,25,26,100,114] These genotoxic effects were found to result in release of cytokines and chemokines from primary cultured vascular smooth muscle and human endothelial cells by our group.[17,75,77,78,100,101,106] molecules required for transformation, growth and differentiation of macrophages/monocytes, vascular muscle and endothelial cells in the evolving atherogenic process.[11–13,109] Supplemental, elevated dietary levels of Mg ameliorate/inhibit the latter transformations, at least in experimental animals.[25,26,100,101,106]

P53, DNA damage and epigenesis

Another, important, critical molecular trigger in the evolving atherosclerotic process is activation of the tumor suppressor gene, p53, particularly in the advanced stages of atherosclerosis.[115–117] DNA-damage is thought to be the trigger for activation of p53.[116] This latter event starts a sequence that regulates growth arrest, cell senescence, apoptosis and programmed cell death of the vascular smooth muscle cells. Using rabbits fed low-Mg-high cholesterol diets, we have reported, with histochemical techniques, plaques containing elevated levels of p53.[118] Not surprisingly, using rats subjected to 21-days of Mg deficiency, we found that cardiovascular tissues and cells of these animals demonstrated 6-8x up-regulation of p53 along with growth arrest, cell senescence, apoptosis, and several forms of programmed CD (i.e.,apoptosis, necroptosis, pyroptosis, and ferroptosis).[91,100,104,119–122] all events found in diverse forms of atherogenesis.[13,14] As stated above, we have found considerable evidence to prove that Mg deficiency induces oxidation of DNA,[11,12,91,100,123] fragmentation of DNA, histone alterations and methylation of the DNA all events clearly demonstrating epigenetic changes in the genomes of the Mg deficient cardiac and vascular smooth muscle cells.

PKC isozymes and cell transformations

PKC isozymes are well-known to regulate morphology, anchorage dependence, and cell tumorigenicity.[124–129] Activation and over-expression of PKC isozymes, in low Mg^{2+} environments, would be consistent with a role for one or more PKC isozymes in transformation of phenotype of macrophages (to monocytes) and contractile vascular smooth muscle cells to a secreting phenotype (as we have observed in animals fed low Mg with high cholesterol diets).[27] Using isolated aortic, cerebral and coronary vascular smooth muscle cells, we have found that low Mg^{2+} environments activate a number of biochemical pathways[130–133] to promote vasospasms including PKC isozymes, which if inhibited by specific antagonists, reduce markedly the contractile/vasospastic actions induced by low Mg.[130–133]

As predicted, exposure of rats and rabbits to low Mg diets, in our labs, resulted in a 6-10x upregulation of PKC isozymes (i.e., classical, novel, and atypical PKC types) In excised aortic, cerebral and coronary arterial muscle cells from these animals, PKC-zeta demonstrated the greatest upregulation.[29,100,114,134] These findings were confirmed in examination of primary cultured aortic and cerebral vascular smooth muscle cells exposed to low Mg^{2+}.[100,134] It is, thus,

tempting to speculate that these up-regulations of several PKC isozymes probably play important roles in the cell transformation of macrophages (to monocytes) and contractile arterial smooth muscle cells to secreting machine cells in the inflammatory and atherogenic processes, in cardiac patients, drug-resistant hypertensive patients, and stroke patients ,who have consumed low Mg diets for several decades.

The DNA alterations, such as oxidation, methylation and histone modifications, we have found in cardiac cells and arterial muscle cells ,excised from animals fed Mg deficient diets, along with up-regulation of proto-oncogenes, NF-kB, and several PKC isozymes, certainly would support our hypothesis that long-term dietary Mg deficiency could give rise to a genotoxic state, thus causing typos in DNA and atherogenesis leading to coronary arterial vasospasm, myocardial infarction, coronary arterial disease, ischemic heart disease, cardiac failure, stroke, and/or SDIHD.

Conclusions

In this presentation, we present a novel hypothesis indicating the probable critical role of Mg deficiency as a genotoxic agent in the development of inflammation-atherogenesis in the cardiovascular system to substantiate how Mg deficiency, over a period of time, triggers a series of molecular-biochemical -signaling events, step-by-step, that could account for growth and transformational changes in vascular smooth muscle cells, endothelial cells, macrophages and monocytes, all necessary for the inflammatory-atherogenic process. This report also reviews how deficient the North American, European, and The UK populations are at the present time, increasing the risks for ischemic heart disease, coronary artery disease, myocardial infarctions, atherosclerosis, sudden-death ischemic heart disease, and strokes.

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Conflicts of interest

The author declares there are no conflicts of interest.

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