Review Article
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Dietary deficiency of magnesium up-regulates several Notch proteins, p53, N-SMase, acid-SMase, sphingomyelin synthase and DNA methylation in cardiovascular tissues: relevance to etiology of cardiovascular diseases, *de novo synthesis of ceramides, down-regulation of telomerases, epigenesis and atherogenesis*

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Introduction

Disturbances in diet are known to promote lipid deposition and accelerate the growth and transformation of smooth muscle cells (SMCs) in the vascular walls.[1,2] Over the past, approximate five decades, a considerable number of reports have appeared to indicate that a reduction in dietary intake of magnesium (Mg), as well as low Mg content in drinking waters, are important risk factors for myocardial infarctions, coronary arterial disease, ischemic heart disease (IHD), sudden cardiac death, sudden-death ischemic heart disease (SDIHD), hypertension, widening of pulse pressure, type 1 and 2 diabetes mellitus, polycystic ovarian syndrome in women (PCOS), preeclampsia-eclampsia in pregnancy, gestational diabetes, blood pressure alterations with dialysis, vaso-occlusive diseases (i.e., sickle cell disease; bowel ischemia; deep vein thromboses), cardiovascular-linked inflammatory disorders, cardiovascular dysfunction in audiogenic stress, and strokes (including those seen in substance abuse), among other cardiovascular diseases worldwide.[3–81] Exactly what mechanisms Mg deficiency is responsible for causing high risks for these diseases is not totally clear. However, it is known that hypermagnesemic diets and/or Mg supplementation does, in many cases, either prevent or ameliorate the dangerous symptoms and downhill courses of events, thus attenuating morbidity/mortality.[26,67] One of the prime reasons for the latter is thought to be reductions in atherogenesis.[11,25,36]

Notch signaling pathways and cardiovascular disease and homeostasis: interactions with Mg and transcription factors

Over the past few years, a pathway originally discovered in *Drosophilain 1913 (The Notch pathway, due to a change in the wings)*, has now become important in mammalian cardiovascular homeostasis and disease.[82–87] It has now become apparent that the Notch gene regulatory pathway plays an important role in vascular smooth muscle cell phenotypes, vascular remodeling and repair after cell injury. Notch ligand binding leads to an intracellular domain (i.e., NICD) which is released from the endothelial cell membrane by a gamma-secretase-dependent proteolytic cleavage of the Notch receptor. Notch signaling from tumor cells has been shown to activate the endothelial cells and thus initiate angiogenesis. Over thepast 15 years, a great deal of attention has been brought to bear on development of gamma-secretase inhibitors.[82–87] Due to the Notch pathway's interaction with the tumor suppressor gene, p53, and other transcription factors, we have speculated that Mg deficient states may act as genotoxins to activate one or more of the four Notch pathways.[88] Using rats exposed to dietary deficiency of Mg for 21 days, we have indeed found that ventricular, atrial and vascular SMCtypes, derived from these Mg deficient animals, demonstrate 3-8x up-regulation of at least three of the Notch gene pathways, viz, 1,2, and 3.[88] In addition, we have noted a strong correlation ($P<0.001$), in the Mg-deficient tissues and cells between activation of several enzymes in the sphingolipid pathway (which generate ceramides and other phospholipids; see below), p53, DNA oxidation and fragmentation, and down-regulation of telomerase, all important factors in atherogenesis.[88]

Reduced daily dietary intake of Mg, cardiovascular disease, and coronary arterial vasospasm

At present, the average daily dietary intake of Mg is from 135-238 mg Mg, while at the turn of last century the intake of Mg was between

450-550 mg/day in North America.[37,58,67] Interestingly, the myocardial level of Mg has consistently been observed to be significantly lower in subjects dying from IHD and sudden death ischemic heart disease (SDIHD) in soft water areas than in subjects living in hard-water areas.[5,7,19,20] Using animal and human isolated coronary arteries, our laboratories were the first to demonstrate that reductions in $[Mg^{2+}]_o$ resulted in intense vasospasm; the lower the Mg^{2+} and the smaller the coronary artery, the greater and stronger the vasospasm;[9,10,12] circulating constrictor hormones (i.e., catecholamines, peptides, serotonin, etc) were vastly potentiated in strength.[10,89] Many of these results were confirmed by other investigators in humans in-vivo.[90–94]

Reduced blood and cellular levels of ionized Mg in cardiovascular diseases, and pregnant women: vascular remodeling and Notch

Using sensitive, specific Mg2+ electrodes, it has been shown that patients with IHD, coronary arterial diseases, SDIHD, strokes, types 1 and 2 diabetes mellitus, preeclampsia-eclampsia, polycystic ovarian syndrome (PCOS), vaso-occlusive diseases, and atherosclerosis exhibit a significant depletion of serum, whole blood, and plasma ionized Mg levels, but not necessarily total Mg levels.[29,31,33,34,36,37,38,41,43,46,47,39,50,54,58,61,65,68–71,74–78,80,81] Cellular and interstitial levels of ionized Mg are also reduced in several of these diseases.[95,96] We have demonstrated considerable vascular remodeling in hypertensive and atherosclerotic animals where cellular ionized Mg levels show significant deficits.[15,23,25,26,28,36,37,38,41,44,58,61,65,68,76,77,78,81] Our preliminary experiments, using primary cell culture of neonatal piglet coronary arterial smooth muscle cells, exposed for 48-96 hours to low [Mg2+]0 demonstrate activation of Notch 1and 2 concomitant with geometrical alterations of cell shapes and apoptosis, thus suggesting evidence for epigenetic changes in smooth muscle cell phenotypes [unpublished findings].

Cellular ionized Mg levels modulate membrane phospholipids, second messengers, activation of multiple intracellular transcription molecules, and membrane transport: relation to epigenesis

Approximately 25 years ago, two of us, using cerebral and peripheral vascular SMCs (VSMCs) in vitro and in primary cell culture, showed that variation in free Mg^{2+} caused sustained changes in membrane phospholipids and second messengers as well as the activation of intracellular transcription molecules (i.e., NF-kB; c-fos, c-jun, MAPK, MAPKK, PKC isozymes, tyrosine kinases, and platelet-activation factor-PAF).[97–106] Such paradigms, using variations in Mg^{2+} also causes membrane oxidation, truncation of membrane fatty acids, activation of several cell death pathways, release of mitochondrial cytochrome C, regulation of subcellular levels of calcium ions, and significant activation of several enzymes in the sphingolipid pathway (i.e, Neutral sphingomyelinase-N-SMase; acid-SMase, sphingomyelin synthase; ceramide synthase).[9,26,28,29,37,44,47,58,88,89,97,98,99,100,105,106,109,110–118] In addition, we found that Mg^{2+} modulates transport of K^+ and Ca^{2+} in vascular muscle cells , cardiac muscle cells, and capillary endothelial cells as well as intracellular release.[26,37,44,58,99,100,109,110,111,113,116–123] Extracellular ionized levels of Mg also control the distribution of Ca^{2+} in subcellular organelles (i.e., mitochondria; lysosomes; nucleus; nucleolus).[116,118] We believe, taken together, our studies provide evidence that alterations in ionized Mg play important roles in epigenesis (see more below).

Importance of dietary Mg intake to modulation of p53 in cardiovascular tissues: potential role in atherogenesis, Notch up-regulation, and epigenesis

The tumor suppressor protein p53 is a key transcription factor that can be activated by numerous agents, including DNA damage, ionizing radiation, ultraviolet irradiation, ribonucleoside triphosphate depletion, metabolic stress, and aging as well as myocardial infarction, reperfusion injury, ischemia, atherogenesis, and stroke.[124–127] Our laboratories have found that cellular depletion and dietary deficiency of Mg are powerful up-regulators of p53 and Notch 1,2 and 3 in cardiovascular tissues and cells.[88,105,106,128]

We have also reported that up-regulation of p53 in Mg deficiency is tied rather closely to Notch proteins regulation, DNA methylation and histone changes in diverse cardiovascular cells.[88] Atherosclerotic plaques demonstrated increased expression of p53 activation, DNA damage, activation of DNA repair pathways in both animal and human arterial vessels and apoptosis. Taken together with our findings that short-term dietary deficiency of Mg, in intact rats, leads to DNA fragmentation, oxidation and diverse forms of cell death in ventricular, atrial, and arterial smooth muscle cells,[129–133] we believe, rather strongly, that Mg deficiency causes epigenesis, which is tied to Notch pathways, in the cardiovascular system resulting in diverse cardiovascular diseases.[134]

Key roles of activation of N-SMase, acid-SMase, ceramide synthase, and sphingomyelin synthase in production of ceramides in cardiovascular tissues and cells in Mg deficiency: relevance to Notch activation

The *de novo* synthesis of sphingomyelin (SM) is brought about via the action of serine palmitoyl-CoA transferase (SPT), 3-ketosphinganine reductase, ceramide synthase (CS), dihydroceramide desaturase, and SM synthase (SMS).[135] SMS requires phosphatidylcholine (PC) and ceramide as substrates to manufacture SM and diacylglycerol (DAG).[135] This reaction directly affects SM, PC, and ceramide as well as DAG levels. We have shown, using primary cell cultures of cerebral, coronary and peripheral vascular muscle cells, that a variation of extracellular free Mg ions ($[Mg^{2+}]_0$) influences the cellular levels of SM, PC, DAG, NF-kB, proto-oncogenes, and ceramides.[29,37,98,99] Ceramides, either released or as a consequence of SMases acting on SM or activation of SPT 1 and 2, CS, or activation of SMS, is now thought to play important roles in fundamental processes such as cell proliferation, membrane receptor functions, angiogenesis, microcirculatory functions, immune-inflammatory responses, cell adhesion, cell motility, atherogenesis, senescence, and programmed cell death.[58,68,105,106,129–131,136–147] Although the activation of neutral- and acid-SMases, SPT 1and 2 (the rate-limiting enzymes for the biosynthesis) by low $[Mg^{2+}]_0$ results in (and ensures) ceramide production in cardiovascular cells and tissues,[106,107] the activation of CS and/or low $[Mg^{2+}]_0$ results in additional levels of ceramides.[106,147] Since SMS activity exhibits links to cell membrane structures and numerous cellular functions,[135,148–151] it could have far-reaching effects on the cardiovascular system. We have found a positive correlation of low Mg-induced activation of Notch 1,2 and 3 to activation of N-SMase, acid-SMase, SPT 1 and 2, and CS as well as increased production of ceramides.[88]

We have shown that even short-term Mg deficiency in: 1. Intact animals and humans up regulates SMS activities in cardiac and

vascular smooth muscle cells; 2. Vascular SMC incubated with inhibitors of SMS and low Mg demonstrate reduced cellular levels of ceramides.[106,128] The other ceramide pathways mentioned, above, also result in generation and release of ceramides when cardiac and vascular smooth muscle cells are incubated with low levels of extracellular free Mg^{2+}.[104,106,147]

Importance of release and generation of ceramides and platelet-activating factors on cardiac and vascular smooth muscle cells: direct actions on cardiovascular pathophysiology, functions, Notch proteins, atherogenesis, and epigenesis

Approximately 50 years ago, utilizing isolated, diverse mammalian blood vessels, and intact in-situ microcirculatory arterioles, precapillary sphincters, and muscular venules in intestinal, skeletal muscle and cerebral vascular beds of rats, dogs, rabbits and guinea-pigs, we reported that diverse ceramides, other sphingolipids, and phospholipids such as platelet-activating factors (PAFs), caused contraction/vasospasm or vasodilation of the large and microscopic blood vessels.[9,10,12,14,15,16,26,28,35,36,37,47,58,68,81,89,99,101,102,105,106,109-116,120,139,152] Similar results have been reported by others, but to a limited extent.[53,153,154] We found, especially, in the intact brain cerebral and medullary microcirculations that even very small concentrations of diverse ceramides and PAFs would result in adherence of macrophages and monocytes on postcapillary endothelial walls, followed by rupture of postcapillary venules and transudation of leukocytes, macrophages, monocytes, and red blood cells into the parenchymal tissues.[142] The latter resembled a small, local hemorrhagic stroke. Histochemical examination of arterial blood vessels,in rabbits fed Mg-deficient diets with cholesterol for 4-12 weeks, revealed not only heavy plaques, but that these plaques contained monocytes, ceramides, PAFs, p53, and altered vascular SMC with signs of TNF-alpha.[23–25,106] In addition, the arterial SMC demonstrated DNA oxidation, telomerase down-regulation, and DNA methylation.[134,155] We believe these findings provide presumptive evidence, with the above for the concept that Mg deficient diets not only can induce atherogenesis but alterations in vascular smooth muscle cells/macrophages which have been observed in human tissues undergoing epigenesis. Whether or not the Notch family of genes, which we have found to be up regulated in Mg deficient animals, are key pathways in atherogenesis-related Mg deficiency remains to be investigated.

Over expression of Notch and proto-oncogenes in magnesium deficiency: potential relationship to pre-eclampsia-eclampsia, gestational hypertension and growth retardation in pregnant women

Approximately 40 years ago, three of us reported, using human umbilical arteries and veins, that low levels of $[Mg^{2+}]_0$ caused these vascular SMC to go into contraction; the lower the external Mg, the greater the spasms.[16,106] At that time, we suggested that low dietary intake of magnesium in pregnant women could result in hypertension, pre-eclampsia-eclampsia, and growth retardation in fetuses [14]. Some years later, using ion-selective electrodes and ^{31}P-NMR spectroscopy on sera and red blood cells from women with gestational diabetes, hypertension in pregnancy, and pre-eclampsia-eclampsia, we reported serum and intracellular levels of free ionized Mg were reduced markedly with concomitant elevation in free ionized Ca^{2+} and increased Ca^{2+}/Mg^{2+} ratios.[38]

During the past 10 years, several investigators have reported that overexpression of Notch proteins in mice and zebrafish have caused several different mutations in bone development, T-cell homeostasis, lymphoid development, erythroid differentiation, and cardiac development.[156–163] Ten years ago, using rats subjected to 21 days of dietary Mg deficiency, we found numerous alterations in sphingolipid metabolism, PAF, PKC isozymes, PI3 enzymes, MPK, MPKK, cytokines, chemokines, and cell signaling in cardiovascular tissues and cells.[97–108,118,128,129,147] What was striking, we found up-regulation of the proto-oncogenes c-fos and c-jun,[58,78,99,105,106] important nuclear cell growth regulators. We, thus, believe that our finding of over expression of Notch 1, 2, and 3, in Mg deficient cardiovascular tissues and cells concomitant with up-regulation of proto-oncogenes, may, in large measure, be responsible for gestational hypertension, pre-eclampsia-eclampsia, gestational diabetes, and growth retardation of fetuses in some pregnant women. We hope our hypothesis will be fully investigated in the near future, particularly as more than five million fetuses are lost worldwide annually.

Conclusions and future thoughts

In this presentation, we have attempted to review a considerable amount of human and animal studies implicating Mg deficiency in the etiology of a number of cardiovascular diseases (CVD) and their patho-physiologies. It seems quite clear from a review of the massive amount of information accumulated, over the past 50-some -odd years, that dietary deficiency of Mg plays multiple roles in atherogenesis, CVD and strokes, and pregnancy. Unfortunately, although thousands of reports and symposia have been published on different aspects of CVD and strokes, Mg deficiency as a genotoxin has not, as yet, been taken seriously as it should be. Many CVD patients have, on their own, through anecdotal means, been aided considerably by increasing dietary intake, supplementation and or water intake of elevated Mg levels. Through careful and persistent investigations by ourselves and others, we believe dietary Mg deficiency should be carefully taken into consideration by all practicing physicians and ER personnel when examining patients for CVD.

Since tremendous shortfalls exist in dietary intake of Mg (as much as 65%) , with the sizeable loss in Mg via food processing, and depletion of Mg in soils by large-scale fertilization with phosphates, we suggested more than 15 years ago, that water intake (e.g., from tap waters, well waters, bottled waters, and beverages using tap/well waters) in humans varying between 1 and 2 l/day, with Mg^{2+} intakes varying from <5 to >100 mg/l, may represent an excellent way to overcome and control marginal intakes of Mg obtained with most Western diets.[58,61,88,104,106,107,128,129,147] In addition, in view of our previous clinical and animal studies, and those reviewed, herein, it is probably propitious to suggest that all desalinated-purified recovered waters, and all bottled waters given to humans should be supplemented with bio available Mg^{2+} to ameliorate/prevent the induction of cardiovascular risk factors and disease processes worldwide.

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Conflicts of interest

The author declares there are no conflicts of interest.

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