

Emerging role of epigenetics in cardiovascular diseases: importance of ionized hypomagnesemia

Short communication

In 1988, Barker and Osmond suggested that suboptimal intrauterine development could produce a predisposition to cardiovascular disease (CVD) in adulthood.¹ This led to the “concept of developmental origins of health and disease”.¹ Since Barker and Osmond’s concept, a considerable amount of animal and human studies has been undertaken to gain insight into the exact mechanisms underlying the developmental programming leading to CVD[see 2, for review]. This work has established that early intrauterine developmental programming is dependent upon, what has been termed developmental involvement of “epigenetic regulation”.² It has been suggested that insults such as poor nutrition, hypoxia, microbial toxins, environmental factors, and diverse chemical agents will increase the risk for CVD and metabolic disorders later in life such as type 2 diabetes mellitus, metabolic syndrome, hypertension, ischemic heart disease (IHD), sudden death ischemic heart disease (SDIHD) and strokes.²

In 2001, Hales and Barker developed the “thrifty phenotype hypothesis” to explain this phenomenon.³ Even though the precise explanation(s) for this developmental phenomenon is not known, certain factors have been found that clearly contribute to explain this phenomenon such as DNA methylation, histone modifications, and micro-RNAs which appear to confer levels of gene regulation without altering sequences in DNA[for reviews, see 3,4]. So far, DNA methylation is the only known factor to cause epigenesis.³ Histones are major regulators of chromatin.³ Micro-RNAs target mRNA which is involved in regulation of protein synthesis.³

Ever since we discovered, in the late 1960’s, that reduction in the level of extracellular magnesium ions ($[Mg^{2+}]$) could cause powerful contractions and spasms of coronary, cerebral and peripheral blood vessels, including intrauterine vessels, excised from diverse animals and human beings, along with increased vascular reactivity to neuro-humoral constrictor agents,⁵⁻²¹ we have thought that dietary deficiency of Mg could lead to development of CVDs later in life and that Mg deficiency could be termed “genotoxic”.²² In order to gain insight into our hypothesis of the critical importance of adequate dietary intake of Mg in development of CVDs, we have recently measured the levels of DNA methylation, histone modifications and micro-RNAs along with the levels of telomerase in ventricular, atrial and vascular smooth muscle cells (i.e., coronary, cerebral, mesenteric, aortic, etc.) excised from rats placed on different Mg-deficient diets for up to 21 days[for review, see 23].

In addition, using newly designed specific, sensitive electrodes to quantify serum, whole blood, plasma and cerebral spinal fluid ionized Mg levels,²⁴⁻³¹ we measured $[Mg^{2+}]$ in bloods and CSF of women throughout pregnancy and at delivery in healthy and preeclamptic women, as well as in women with diseases specific to women (e.g., gestational diabetes; menopause; PCOS; ovarian hyperstimulation)³²⁻⁴⁷ and newborn healthy and diseased infants.^{27,28,30,34,43,48}

So far, our data clearly show that cardiac and vascular smooth muscle cells excised from rats placed on Mg-deficient diets for up to 21 days reveal upregulation of DNA methylation, histone

Volume 4 Issue 6 - 2019

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Received: December 14, 2019 | **Published:** December 23, 2019

modifications, oxidation of DNA, upregulation of several micro-RNAs, and downregulation of telomerases.^{23,49,50} Measurement of blood levels of Mg^{2+} in pregnant women up to term pregnancy demonstrated a gradual reduction in serum Mg^{2+} ; women who developed transient hypertension at birth showed further reductions in serum levels of Mg^{2+} ,^{32,33,36-38,40,41} along with alterations in cerebral spinal fluid levels of Mg^{2+} .⁴⁶ Some newborn infants were found to have developed pulmonary hypertension, in utero, and these babies demonstrated lowered serum levels of Mg^{2+} on delivery. We believe these preliminary data are enough, so far, to implicate Mg deficiency as a “genotoxic agent” and a causal factor in potential development and aberrant epigenesis and CVDs. Mg^{2+} is a critical requirement for over 500 different enzymes in the body which regulate protein synthesis, and metabolism of carbohydrates, lipids, phospholipids, nucleotides, DNA, and RNA, as well as excitation-contraction coupling of all muscle cells, nerve excitation, and membrane transport of key ions and solutes.

Conclusions and future thoughts

During the past decade, a considerable amount of experimental and clinical data has appeared to implicate that the epigenetic code can provide a link between prenatal stress and alterations in gene expression that might alter developmental programming of various diseases later in life. More than 50 years ago, two of us found that reductions in extracellular ionized Mg levels, both *in-vivo* and *in-vitro*, would cause coronary, cerebral, peripheral and uterine blood vessels to go into spasm and demonstrate increases in vascular reactivity to neuro-humoral constrictor agents and circulating vaso-peptides. Dietary deficiency in rats resulted in methylation of DNA, histone modifications, increased levels of certain micro-RNAs, and oxidation of DNA as well as a downregulation in telomerases in cardiac and vascular muscle cells. Using specifically-designed, sensitive electrodes for measurement of blood ionized levels of Mg, we found

that pregnant women demonstrate reductions in blood levels of Mg^{2+} towards term with some women who developed transient hypertension and gestational diabetes demonstrating further reductions in serum Mg^{2+} . Some infants at birth presented with pulmonary hypertension and lowered serum ionized Mg. We believe these new experimental and clinical observations provide presumptive evidence that dietary deficiency of Mg can lead to epigenetic alterations in cardiac and vascular muscle phenotypic alterations which could induce CV diseases such as hypertension, diabetes, IHD, SDIHD, preeclampsia, neonatal pulmonary hypertension, and other syndromes. In view of our new studies, all pregnant mothers and babies should be monitored for ionized Mg levels and treated accordingly.

Acknowledgments

Much of our animal and human studies were supported, in part, by research grants from The National Institutes of Health (i.e., National Heart, Lung and Blood Institute; The National Institute on Mental Health; The National Institute on Drug Abuse; and The National Institute on Alcoholism and Alcohol Abuse) and unrestricted research grants from several pharmaceutical companies.

Conflicts of interest

The author declares there are no conflicts of interest.

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