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Sudden Cardiac Death in Infants, Children and Young Adults: Possible Roles of Dietary Magnesium Intake and Generation of Platelet-Activating Factor in Coronary Arteries

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Abstract

Magnesium (Mg) is a co-factor for more than 500 enzymes, and is the second most abundant intracellular cation after potassium. It is vital in numerous physiological, cellular and biochemical functions and systems necessary for life. Approximately 35 years ago, our laboratory suggested that a progressive, dietary deficiency and/or metabolic induced loss of Mg from the body, beginning early in life, particularly during development of the coronary arteries, could lead to coronary arterial vasospasm, ischemic heart disease, and sudden-cardiac death (SCD). Herein, we review evidence for a brand-new, novel hypothesis which combines knowledge suggesting a combined role for hypomagnesemia and platelet-activating factor (PAF) which may provide insights into unexplained SCD in infants, children, and young adults. This review documents what takes place in the cardiovascular system when the body and its tissues are subjected to lower than normal dietary Mg intake, and also provides new evidence for a series of heretofore unknown actions of PAF that are most likely involved and/or trigger coronary arterial vasospasm in the presence of low concentrations of ionized Mg levels. The roles of vascular remodeling, NF-κB and proto-oncogenes are considered to play major roles in this hypothesis.

Keywords: Magnesium deficiency; SIDS; Atherogenesis; Nuclear factor-κB; Proto-oncogenes; Coronary vasospasm; Cardiovascular diseases; PAF

Introduction

Approximately 35 years ago our laboratory suggested that a progressive, dietary deficiency and/or a metabolic-induced loss of magnesium (Mg) from the body beginning early in life, particularly during development of the coronary arteries, could lead to coronary arterial vasospasm, ischemic heart disease, and sudden cardiac death (SCD) [1,2]. Ever since this work was published, a number of clinical studies have been done and published which support this hypothesis, at least in adults [3-10]. However, little or no studies have been published to either confirm or deny this hypothesis in either infants or young children.

Autopsies of children, who have died as a consequence of accidents, have often demonstrated early signs of atherogenesis (e.g., fatty streaks on the walls of the aorta and carotid arteries in young children as early as six years of age) [11]. It should be noted that atherosclerosis is the number-one cause of premature death in developing countries, including the United States and plays a major role in etiology of hypertension and strokes.

Disturbances in diet are known to produce inflammatory lesions, promote lipid deposition and accelerated growth, and transformation of the smooth muscle cells in the vascular walls [11-16]. Reduction in dietary Mg intake has been demonstrated, experimentally, to result in hypertension [17-20], atherogenesis [15,21-27], and stroke [15,27-34]. Hypermagnesemic diets have been shown to ameliorate hypertension, atherogenesis, stroke and certain inflammatory responses [34-41]. In the Western World, dietary intake of Mg is subnormal, with shortfalls of between 65 and 225 mg of Mg/day, depending upon geographic region [42,43]. Newly compiled USA NHANES data indicate that approximately 65% of the American population is Mg deficient [44]. Several epidemiologic studies in North America and Europe have shown that children and adults consuming Western-type diets are low in Mg content as are pregnant women (i.e., 30-50% of the RDA for these populations) [42-44].

Low Ionized Mg measurements in Serum: Relationship to Ischemic Heart Disease and Vascular Remodeling

Using sensitive, specific Mg^{2+} - ion selective electrodes, it has been shown that patients with ischemic heart disease, essential hypertension, renal-diseased induced hypertension, and strokes exhibit significant depletion of serum and cellular ionized Mg^{2+}, the physiologically-active Mg [14,25,29-32,45-54]. In addition, we have shown that pregnant women with gestational diabetes, preeclampsia, and difficult labors also demonstrate depletion of serum as well as cellular levels of ionized Mg^{2+} [48,49,52-54]. Such low levels of ionized Mg, when mimicked *in vitro*, result in spasms of peripheral, coronary, placental, neonatal, and cerebral vascular smooth muscle (VSM) cells, rapid cellular influx and intracellular release of free Ca^{2+}, well as increasing vascular reactivity to numerous neurogenic and humoral molecules [2-4,14,19,25-31,55-62]. Dietary deficiency of Mg in rats has been shown to not only cause hypertension [17,20], but to also cause vascular remodeling (i.e., arteriolar wall hypertrophy of unknown origin), rarefaction of capillaries (known itself to result in hypertension) [18], stiffening of arterial walls [20], as well as release of cytokines and chemokines (involved in inflammatory and atherogenic responses) [63-65].

Magnesium Deficiency Results in Activation of NF-κB and Proto-Oncogenes

The nuclear factor-kappa B (NF-κB) and proto-oncogenes (e.g., c-fos, c-jun) are two major regulators of growth, differentiation, cell migration, and cell death (e.g., apoptosis) [66-69]. NF-κB is a transcription factor and a pleiotropic regulator of numerous genes involved in inflammatory responses, hypertension, and atherogenesis [12,66,67,69]. Both NF-κB and the proto-oncogenes are thought to be pivotal in numerous vascular disease processes such as inflammation, atherogenesis, hypertension, and ischemic heart disease [12,66,67,69]. It is, however, not clear as to what initiates expression of these molecular and cellular events, particularly with respect to how Mg deficiency impacts on these vascular events and how low Mg causes (or predisposes to) hypertension, intense vasospasm, inflammation, stroke-like events, cardiac failure , and SCD. Experiments performed *in-vitro* and *in-vivo* on cells and living animals have demonstrated that short-term magnesium deficiency (MgD) results in formation/activation of NF-κB and the proto-oncogenes in cardiovascular tissues and VSM cells [14,25,26,64,65,70].

Sudden Cardiac Death is a Growing World-wide Problem

Sudden infant death syndrome (SIDS) has become a significant problem without an agreed-upon pathological mechanism(s) [71-76]. Explanations run the gamut from hypoxia, gene mutations, cardiac conduction abnormalities, inherited channelopathies, unknown infections, diaphragmatic dysfunctions, central hypoventillation, susceptibility to ventricular arrhythmias, etc.. Pediatric sudden cardiac arrest likewise seems, for the most part, to be a growing problem around the world with little in the way of an acceptable pathogenic mechaism(s) [71-76]. SCD accounts for approximately 20% of nearly all deaths in Western countries with multiple possible, but little agreed-upon explanations. SCD in the young (<35 yrs of age) has a structural/genetic basis in only about 20% of all cases in the Western World. In most of these SCD cases, there is no structural/pathological evidence for any heart abnormalities on autopsies [71-76].

Studies of Isolated Adult Mammalian and Human Coronary Arteries as well as Neonatal Piglet Coronary Arteries demonstrate Intense Vasospasm on Reduction in Extracellular Mg

Approximately 35 years ago, our laboratories reported that mammalian coronary arteries from neonates as well as adults (including those obtained from humans) demonstrate intense vasospasm as extracellular Mg^{2+} ($[Mg^{2+}]_0$) concentrations are lowered progressively in *in-vitro* studies; the lower the reduction in $[Mg^{2+}]_0$, and the smaller the coronary arterial vessel, the more intense the coronary arterial vasospasm [2-4,14,25-31,55-62]. No vasodilator, including Ca^{2+} channel blockers can effectively alleviate these intense coronary vasospasms. These contractile actions of low Mg^{2+} are potentiated in the presence of neurohumoral and circulating vasoconstrictor agents, such as angiotensin II, vasopressin, serotonin, norepinephrine, and a variety of pressor peptides. Coronary arterial vessels, particularly small ones (<100 μm in diameter) obtained from neonatal piglets are exquisitely sensitive to low $[Mg^{2+}]_0$ levels. On the basis of our studies on the neonatal piglet coronaries, we suggested almost 20 years ago, that low $[Mg]_0$ could play an important role in SIDS and SCD [77]. Collectively, such findings lead us to conclude that low dietary Mg levels in pregnant women, infants and children must be taken into consideration as a major underlying mechanism for unexplained SCD in infants, children and young adults.

Low Serum Ionized Magnesium Levels found in Infants and Children in the USA

In view of the above evidence and hypothesis, it is of considerable interest to point out, here, that several studies, including those done in our laboratories, have been published which indicate that infants and children in the USA demonstrate a much higher percentage of abnormally lowered serum total and ionized Mg levels when compared to adults 35-60 years of age [14,45,48,49,78-81]. Moreover, our studies on infants, children and pregnant women have shown a high percentage of abnormally low serum ionized Mg levels as well [14,52-54,82-84]. Taken together, we believe such clinical studies, collectively, provide substantial evidence for our hypothesis that unexplained SCD in infants and children possibly is due, in large measure, to abnormally low serum as well as low VSM and cardiac myocyte Mg^{2+} levels. With respect to the latter, we have shown, working with perfused rat hearts, that even short-term MgD results in reductions in a variety of hemodynamic functions, i.e., cardiac output, coronary flows, stroke volume, developed pressures, and cellular high-energy phosphate levels with concomitant Ca^{2+} overload [85]. In 1996, we demonstrated on hearts excised from rats given low Mg diets that Mg depletion impairs carbohydrate metabolism and lipid metabolism and results in cardiac calcium overload [86]. We showed more than 40 years ago that Mg^{2+} blocks the entry and intracellular release of Ca^{2+} from both VSM and cardiac myocytes [55,57,59,86-88]. This together with the adverse effects on both cardiac hemodynamics and energy production (and utilization) would perforce seriously compromise young hearts and result in SCD.

Is Genesis and Release of Platelet-Activating Factor (PAF) the Major Downstream Signal for induction of Coronary Arterial Vasospasm seen in Low Mg Environments?

Approximately 18 years ago, we reported that reduction of extracellular Mg^{2+} levels resulted in generation of variety PAF-like lipids, as seen with proton nuclear magnetic resonance spectroscopy [87]. At that time, we suggested that one or more of these PAF-like molecules may be an initiator of low Mg^{2+}-induced arterial vasopasm and atherogenesis [87]. Over the intervening two decades, we have found that peripheral, cerebral and coronary arterial vessels, including neonatal coronaries, undergo contraction in the presence of low concentrations ($<10^{-6}$ M) of PAF by acting on specific VSM membrane PAF receptors [88]. Moreover, the intense arterial vasospasms observed as $[Mg^{2+}]_0$ is lowered can be dramatically attenuated in the presence of specific PAF- membrane receptor blocking drugs [88]. In addition, our new findings indicate that as $[Mg^{2+}]_0$ is lowered, a rapid (within seconds) generation and release

of PAF is observed in the cultured VSM cells, including those obtained from neonatal piglets [88]. PAF is now thought to be an important, maybe critical, molecule in etiology of inflammatory conditions and atherosclerosis [89-91]. We thus believe that our new findings suggest major roles for MgD and PAF formation (and PAF-like lipids) in the cardiovascular manifestations of MgD, inflammation, atherogenesis, and SCD in children.

Approximately 40 years ago, Russell Ross and colleagues [92] advanced the hypothesis that atherosclerosis is an inflammatory disease brought about by injury to the endothelial surfaces of blood vessels in the macro- and microcirculations. The hypothesis stated that different forms of injury (including hypoxia and ischemia) will result in numerous dysfunctions in the homeostatic properties of the blood vessels and the underlying vascular smooth muscle cells, e.g., adhesiveness of leukocytes and/or platelets, formation/release of cytokines/chemokines and growth factors; all of these entities needed for atherogenesis are produced in MgD states. We believe low $[Mg^{2+}]_0$ environments act as triggers to induce local hypoxic and ischemic events within the macro- and microcirculations to initiate inflammatory-atherosclerotic sites via initial generation and release of Ca^{2+} and PAF. These events could be expected to take place in developing fetuses in-utero and after birth. Since most diets consumed in the Western World are deficient in Mg by as much as 65% below the RDAs for adults, infants and the young, such circumstances would perforce result in inflammatory conditions, vasospams, atherogenesis, and SCD.

Conclusions

This article reviews the evidence for a brand-new, novel hypothesis which combines evidence suggesting a combined role for hypomagnesemia and PAF which may provide insights into unexplained SCD in infants, children, and young adults. This report not only documents what takes place in the cardiovascular system when the body and its tissues are subjected to lower than normal dietary Mg intake, but provides new evidence for a series of heretofore unknown actions of PAF that are most likely involved and/or trigger arterial vasospasm in the presence of low $[Mg^{2+}]_0$ and probably is a major trigger for unexplained SCD.

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