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Exposure to High Levels of Noise Poses Hazards and Risks for Development of Hypertension and Heart Disease: Potential Roles of Unrecognized Ionized Hypomagnesemia and Release of Ceramides and Platelet-Activating Factor

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Abstract: It has been demonstrated in numerous human and animal studies that audiogenic stress (AS) can induce elevation of arterial blood pressure and cardiac damage and that noise -induced hearing loss may be associated with alterations in magnesium (Mg) metabolism. Our laboratories, over a period of approximately 40 years, have been investigating why AS causes high blood pressure and cardiac damage. This review focuses on a number of newer discoveries on why AS causes dysfunctions of the cardiovascular system (CVS) This review discusses the pivotal physiological and biochemical importance of Mg to body health and the fact that most Americans and Europeans are deficient in daily Mg intake which perforce can cause severe dysfunctions of the CVS. Our ongoing studies clearly provide a solid microcirculatory basis for how and why AS above 65dB(A) often induces elevated blood pressure and cardiac damage. We review a body of data that points to the fact that AS does the latter, but appears to do so because noise stress levels result in Mg deficiency followed by release of certain sphingolipids (e.g., ceramides) and generation and release of platelet- activating factor (PDF). It is our opinion that all people exposed to high degrees of noise stress should be monitored for cardiovascular functions, ionized Mg levels, blood ceramide levels and levels of PDF. Lastly, we believe all people exposed to high levels of AS (i.e., maintenance people and pilots on aircraft carriers, musicians [particularly at rock concerts], motorman and conductors on trains and subways, construction site workers, etc.) should have at least the equivalent daily intake of 500-600 mg of Mg/day.

Keywords: microcirculation, blood pressure, cardiac function, sphingolipids, atherosclerosis, inflammation.

In all industrialized societies, noise is an important environmental and occupational stress factor. There are several pathophysiological reactions to noise that range from hearing loss, annoyance, loss/lack of concentration to several dysfunctional alterations of the cardiovascular system; the latter leading to hypertension, heart attacks, and cardiac failure [1-5]. A high positive correlation has been found between exposure of individuals to noise and high blood pressure in a number of retrospective epidemiological studies [6-11]. Moreover, noise-induced elevation of arterial blood pressure in both rats and human subjects has been associated with increased peripheral vascular resistance and cardiac hypertrophy [10, 12- 16]. Although there is evidence of increased activation of the sympathetic nervous system with release of norepinephrine and epinephrine into the bloodstream during exposure to high levels of noise (i.e., above 85 dB(A), the elevation in blood pressure, during noise exposure, is independent of elevated levels of catecholamines, cortisol, prolactin, or growth hormones [13-17]. In addition, central α_2 -adrenergic receptors do not appear to be involved [16].

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When one thinks about the risks and hazards of prolonged environmental noise exposure, most people only worry about loss of hearing. However, the unrecognized detrimental effects of excessive noise exposure, on the cardiovascular system is almost never thought of when patients present with hypertension and/or heart –coronary artery disease. This is particularly of great concern for navy pilots taking off from aircraft carriers and for the maintenance crews which work on the flight decks where noise levels usual range from 130-165 dB(A) [18]. In addition, in the civilian population, particularly our youth who attend rock concerts , the noise levels can be in excess of 165 dB(A) [4,5]. It should be pointed out that noise stress can produce reactions in the human body similar to stressors such as heat, cold, and shock caused by blood loss and trauma, or psychological causes such as heavy work -loads and intense anxiety/worry [2, 7,9,12,13,19]. How much of the high blood pressure and heart disease seen in the later years of navy pilots and teenagers, attending rock concerts, could be attributed, in part, to excessive environmental noise? What causes the cardiovascular dysfunctions observed in humans and animals exposed to prolonged and excessive noise levels?

NOISE-INDUCED MG DEFICITS AND HIGH BLOOD PRESSURE

A growing body of evidence is accumulating to suggest that there may be a “true” causal relationship between decreased magnesium (Mg) levels in the blood, tissues and cells after excessive noise exposure and development of hypertension [10,11, 19-23 ,59]. It has been observed that the incidence of hypertension is often high in geographic regions with soft-drinking water or Mg-poor soil [24-33]. Hypomagnesemia has, indeed, been reported in a growing number of hypertensive subjects when the blood and tissues are examined for decreased levels of Mg [31,34]. It has been demonstrated in a number of human and animal studies that oral and parenteral administration of Mg can often lower the elevated arterial blood pressures in subjects that present with high blood pressure[27,29-37]. Three of us have clearly shown that dietary deficiency of Mg ,under controlled laboratory conditions, will raise diastolic and systolic arterial blood pressures in a dose-dependent manner and aggravate hypertension in both spontaneously and deoxycorticosterone acetate –salt hypertensive rats; the less the dietary intake of Mg, the higher the blood pressures up-to-a-point [10,32,35-40,60]. These findings have been confirmed by other investigators [41,42]. In numerous in-vivo and in-vitro studies, our group has found that reduced blood and tissue-cell levels of Mg^{2+} causes changes in cell geometry and cellular calcium overload, in all types of cells so far examined [10,29,33,34,37,40 ,43-58]. Such a series of events produces constriction/vasospasm of all types of macro- and microscopic blood vessels [10,26,28,29,32-34,37-40,44,45,47-52 ,53,54,57]. A microcirculatory basis for these important findings has been advanced by our group [10,38,54,59 ,60]. Exposure of laboratory animals to increasing levels of acoustical stress [e.g., from 65 dB(A) to 100 dB(A)] over periods of from eight to 12 weeks for 12hours daily results in reductions in serum Mg levels as well as deficits in cardiac and vascular smooth muscle Mg^{2+} levels in a dose-dependent manner; the longer the acoustical stress and the greater the levels of noise stress, the greater is the rise in systolic and diastolic blood pressures [10, 59, unpublished findings]. Statistical analysis of these data demonstrate very high degrees of correlation between Mg^{2+} levels, degree of noise stress , and rise in arterial blood pressures (i.e., $P < 0. 01$).

IMPORTANCE OF MG TO BODY HEALTH AND BIOCHEMISTRY

Mg is a co-factor for more than 500 enzyme systems, and it is the second most abundant intracellular cation after potassium [61]. It is critical in numerous physiological, cellular and biochemical functions and systems, running the gamut from transmembrane fluxes of cations and anions, hormone-receptor binding, cellular energy generation, muscle contraction, nerve impulse conduction, regulation of DNA and RNA structure, regulation of carbohydrate, protein and lipid metabolism, regulation of plasma lipid levels(i.e., cholesterol, triglycerides, and LDL-cholesterol), regulation of cell and tissue growth, diverse cardiac functions and cardiac stability, regulation

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of blood pressure, control of vasomotor tone and distribution of microcirculatory blood flows to all organ systems, and to cell death (e.g., apoptosis, necroptosis), among others [29,31,37,54,61,64]. Mg is depleted in most methods of food preparation (i.e., boiling, frying, etc.) and processing [60].

The daily intake of Mg has been declining since 1900, from where it was about 500-600 mg/day to about 150-235 mg/day in many USA and European geographic regions at the present time [31, 34, 37, 60-67]. Mg exists in three forms; free or ionized, complexed and protein-bound [36, 68]. These three forms constitute the total serum and cell Mg [36,68]. Up to our extensive studies, there were no reliable methods to rapidly measure the ionized Mg fraction in blood and other body fluids, particularly in the OR and critical -coronary care units [36].

RELATIONSHIP OF MG TO CARDIAC STABILIZATION AND FUNCTION, HYPERTENSION AND NOISE STRESS

An increased risk for development of myocardial infarction and ischemic heart disease (IHD) has been clearly observed under long-term environmental noise stress [11-17,19-21]; the noise level usually has to be above 65dB (A) for these risks to become manifest. These levels of noise stress would be seen with road traffic noise, railroad noise, construction sites, subways, rock concerts, airports, and take-offs and landings from aircraft carriers [18,22,23]. All of these environmental stresses have been observed to be associated with deficits in Mg levels [5, 13,16,19,69].

Using normal, intact rats and perfused rat hearts, we have found that reduced dietary intake of Mg or reduced levels of Mg²⁺ in the perfusates, in isolated working rat hearts, caused numerous detrimental actions on the ability of the hearts to function properly [70-72]. For example, reduction in Mg²⁺ levels resulted in deficits in coronary blood flows, reductions in cardiac output, reductions in stroke volume and peak systolic pressure development, reductions in myocardial intracellular Mg²⁺ levels, reduction in myocardial levels of ATP, increased levels of inorganic phosphate, acidification of atrial and ventricular myocytes, Ca²⁺ overload, and generation of powerful reactive oxygen and nitrogen species (e.g., H₂O₂, hypochlorite anions, hydroxyl ions, ferrylmyoglobin, etc.) [70-72]. Acoustical stress (eg., in excess of 65dB(A) for eight to 12 weeks) resulted in similar pathophysiological effects on rat hearts as did Mg deficiency [72; unpublished findings].

However, when we examined the myocardiums and vascular smooth muscle cells exposed to Mg deficiency, or acoustical stress, we noted unique changes in sphingolipids and sphingolipid metabolism [33,34,73,84,88]. These studies led us into another series of biochemical and molecular pathways which have, we believe, direct bearing on the mechanisms whereby noise stress can lead to high blood pressure and cardiac-coronary artery disease.

Mg²⁺ REGULATES SPHINGOLIPID PATHWAYS IN CARDIAC AND VASCULAR SMOOTH MUSCLE CELLS: RELATIONSHIP TO EFFECTS IN NOISE STRESS

Studies from our laboratories indicate that Mg²⁺ can modulate sphingolipid pathways in both cardiac and vascular smooth muscle (VSM) cells. A product of sphingolipid metabolism is ceramide and related lipids [74,75]. Ceramides are sphingolipids known to be released as a consequence of sphingomyelinases (SMases) acting on sphingomyelin (SM), a component of all extra- and intracellular cell membranes, or as a consequence of the activation of serine palmitoyl transferase 1 and 2 (SPT 1 and SPT 2) (a *de novo* synthetic pathway). Ceramides are known to play important, and key, roles in fundamental pathophysiological processes such as inflammation, angiogenesis, atherogenesis, membrane-receptor functions, cell proliferation, microcirculatory functions, cell adhesion, immunogenic responses, excitation-contraction coupling events in cardiac and VSM cells, and cell

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death (e.g., apoptosis, necroptosis) [74-79]. An upregulation of SPT 1 and SPT 2 has been hypothesized to play important roles in apoptosis and necroptosis events taking place in atherogenesis [80-81]. Such an upregulation could be quite pivotal in producing plaques on the endothelium of coronary arterial blood vessels leading to ischemic events, IHD, and myocardial infarctions. Our studies with cardiac muscle excised from rats exposed to acoustical stress [i.e., 65 dB(A) to 100 dB(A)] for 8-12 weeks, 12 hr/day, showed activation of SMases and formation of ceramides [73].

It is of considerable interest to note, here, that experimentally, myocardial infarctions have recently been found to be associated with rising levels of ceramides [81-83]. In human subjects, it has been reported that stable angina pectoris, unstable angina pectoris, and acute myocardial infarction are also associated with rising levels of ceramides [82, 83]. In some of these patients, a clear elevation in activation of SMases was observed along with a reduction in SM.

During the performance of some of our experiments, with proton-nuclear magnetic spectroscopy, in vitro and in vivo with low $[Mg^{2+}]_0$, we noted a rapid formation of a substance we identified as platelet-activating factor (PAF) along with PAF-like lipid molecules [84].

Mg²⁺-DEFICIENT ENVIRONMENTS AND NOISE STRESS LEAD TO FORMATION OF PAF IN CARDIAC AND VSM CELLS: POTENTIAL SIGNIFICANCE TO NOISE-STRESS -INDUCED CARDIAC DYSFUNCTIONS AND HYPERTENSION

PAF is known to be a major player in inflammatory responses, arterial blood pressure, and atherogenesis among many other physiologic functions [85-87]. In addition, PAF and PAF-like lipids are known to affect the heart and cardiac functions in numerous manners [85-87]. For example, PAF can produce coronary arterial vasoconstriction, alter arterial blood pressure, increase coronary vascular resistance, release several lipid-like molecules from the heart, reduce cardiac output, decrease cardiac contractility, alter atrial and papillary chronotropicity and membrane potentials, as well as alter potassium currents in isolated cardiomyocytes [85-87]. All of these various attributes of PAF on the myocardium would be more than enough to cause profound atrial and ventricular fibrillation, IHD and myocardial infarctions. Moreover, a variety of the circulating blood-formed elements (e.g., leukocytes, platelets, basophils, and macrophages) can also elaborate PAF and PAF-like lipids. Recently, our group has reported that aortic, cerebral vascular and neonatal cardiac myocytes and coronary arterial VSM cells can also elaborate PAF, particularly when these cells are exposed to low $[Mg^{2+}]_0$ levels [88]. Examination of microcirculatory blood vessels utilizing our TV image-intensification recording system with application/administration of PAF showed that this vasoactive lipid produced increased leukocytic adhesion on the endothelial walls, less rolling of leukocytes, and increased permeability of the postcapillary microvessel walls [88]; ceramides produced almost identical results [79]. We believe when these new data are viewed, in light of our other work, reviewed above, they could be used to advance the hypothesis that continued, acoustical stress-induced loss of tissue and cell Mg^{2+} , over months and years, would lead to release of ceramides, PAF, and PAF-like lipids which could result in hypertension, cardiac ischemia followed by IHD, and myocardial infarction. If these pathophysiologic situations were coupled to dietary deficiency of Mg, the effects on the cardiovascular system would be quite profound. Obviously, this hypothesis remains to be tested rigorously in human subjects. However, at the very least, we believe it would be propitious to supplement diets of human beings with enough Mg to cause a total intake of between 550-600 mg/day, particularly among subjects who are continually (i.e., daily for extended periods of time) subjected to high levels of acoustical stress.

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CONCLUSIONS AND FUTURE THOUGHTS

Although the exact cause(s) of noise-induced hypertension, IHD and related myocardial infarctions is not known, Mg^{2+} -depletion is clearly observed in experimental animals and humans exposed to noise levels in excess of 65 dB(A) for prolonged periods of time. The greater the degree of acoustical stress, and the longer the time for exposure, the greater the loss of serum and tissue Mg, at least in experimental animals. Generation/release of sphingolipids (particularly ceramides), PAF and PAF-like lipids appear to be critically involved in the cardiovascular effects of prolonged acoustical stress, at least in experimental animals. These molecules should be looked for in humans exposed to road traffic noise, construction-site noises (e.g., particularly with prolonged use of jack-hammers), motorman and conductors on trains and subways, airports, and especially pilots and maintenance crews on aircraft carriers. In order to test our hypothesis, animals and clinical trials on human subjects, exposed to the latter environmental changes, should be administered in some studies : 1. Inhibitors of SMases and SPT 1 and 2; 2. receptor blockers of PAF on cardiac and VSM muscle cells; 3. exposure to the latter and former together; and 4. supplementation with orally-administered Mg compounds. We also believe all human subjects that present with high blood pressure and/or IHD and myocardial infarctions should be routinely tested for blood levels of ionized Mg, as the latter is the physiologically-active form of Mg, not total serum Mg [36, 68].

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