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Why is Alcohol-Induced Atrial Arrhythmias and Sudden Cardiac Death Difficult to Prevent and Treat: Potential Roles of Unrecognized Ionized Hypomagnesemia and Release of Ceramides and Platelet-Activating Factor

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Abstract

Heart failure is the leading worldwide cause of morbidity, myocardial infarctions and mortality whose causes impose staggering costs and often lengthy hospitalizations. The specific reasons (or mechanisms) to explain or predict atrial arrhythmias in alcoholics or" binge- drinkers" are not known. The authors present evidence for a novel, new hypothesis whereby low tissue and serum levels of ionized magnesium(Mg^{2+}) coupled to release of ceramides and platelet-activating factor (PAF) act to increase risk for cardiac atrial arrhythmias in people who imbibe too much alcoholic spirits over a short-period of time(i.e., binge-drinkers) or are alcohol abusers. The authors discuss several mechanisms whereby low Mg^{2+} and the generation of PAF and ceramides produce a high probability for atrial arrhythmias in alcoholics. The importance of adequate water-borne and dietary levels of Mg is emphasized.

Keywords: Alcohol abuse; Sphingolipids; PAF; Ionized magnesium; Microcirculation

Introduction

Numerous epidemiological studies have suggested that ingestion of daily low concentrations of alcohol (e.g., 1-2 drinks) might be cardioprotective [1-3]. In contrast, high doses of ethanol are known to pose risks for atrial fibrillation (AF) and arrythmias, supraventricular arrhythmias, angina, ischemic heart disease (IHD), hypertension, strokes and sudden cardiac death (SCD) [4-7]. Although numerous hypotheses have been advanced to explain alcohol-induced AF and SCD, such as genetic predisposition, underlying QT abnormalities, alterations in calcium homeostasis, underlying electrolyte abnormalities, baroreceptor disturbances, nutritional abnormalities and cardiac muscle structural changes, satisfactory explanations are still lacking [5-9]. Exactly why female adults, prior to menopause, demonstrate one-third the rate of alcohol-induced hypertension, AF and SCD is also not known [10,11].

Alcohol abuse leads to primary malnutrition that is deficient utilization of nutrients. Alcoholic beverages provide what is termed "empty" calories because ethanol does not contain significant amounts of proteins, vitamins, or minerals. An individual who consumes 5 to 30 ounces of an 86-proof (43% v/v ethanol) beverage will ingest from 375 to 2,250 empty calories. In other terms, this represents from as little as 15% of the normal daily caloric requirements to 100%. The end result of such intake is a decreased intake of other foods and results in an imbalance of daily nutrient ingestion [12]. Serum hypomagnesemia occurs in from 30 to 60% of the alcoholic population [13-16]. Nearly 90% of patients undergoing alcohol withdrawal are hypomagnesemic.

As early as the beginning of the nineteenth century, alcohol abuse was found to be detrimental to the heart. In 1902, MacKenzie coined the term "alcoholic heart disease" [17]. Approximately 50 years later, William Evans reported on characteristic T-wave changes and the presence of AF, paroxysmal atrial tachycardia, and bundle blocks [18]. Ettinger and co-workers, in 1978, coined the term "holiday heart" which is defined "as an acute cardiac rhythm and or conduction disturbance associated with heavy ethanol consumption in a person without any other clinical evidence of heart disease and disappearing without evident residual disturbances, with abstinence" [19]. However, the most common arrhythmia found in this original study was AF. A Framingham study of more than 10,000 people reported, in 2004, that long-term consumption of alcohol (> 35 g alcohol/day) resulted in a high risk (e.q., more than 30%) for AF, and strokes, and SCD [20]. Interestingly, a prospective cohort study in Denmark of nearly 50,000 men and women also found heavy consumption of alcohol resulted in a very high risk for AF, but with one difference women consuming daily alcoholic beverages demonstrated a very low risk for AF [21]. Overall, looking at additional studies as well, there is a clear relationship between heavy alcohol ingestion (i.e., 3-5 drinks/day), AF and SCD [2-7]. A similar relationship with "binge-drinking", AF and SCD is also clear. In most of these subjects, the only findings at "post mortem" are fatty livers typical of heavy alcohol ingestion, often leading pathologists, inaccurately, to term the SCD to alcohol-induced liver toxicity, rather than "alcohol-associated arrhythmic death". Less than 15% of these deaths have been associated with either a history of IHD or atheromas on the coronaries on autopsy [6,7]. This has led most pathologists to misdiagnose the actual cause of AF-induced SCD [7].

Over the past two decades, evidence has accumulated to indicate that daily dietary deficiency in magnesium (Mg) intake and/or

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errors in Mg metabolism poses serious risks for development of AF, hypertension, IHD, and SCD [22-37], whereas higher than normal Mg intake is found to be associated with decreased or ameliorated AF, myocardial infarctions, hypertension, strokes, and incidence of SCD [14,24-36]. It has been known for more than 40 years that chronic ingestion of alcoholic beverages results in body depletion of Mg [6,7].

Relationship of Mg to Cardiac Stability, Function, IHD and SCD: Importance of Ionized Mg

Mg is 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 reactions including carbohydrate, lipid, protein, DNA, and RNA metabolism, among other pathways [24,38]. Several epidemiologic studies in North America and Europe have shown that people consuming Western-type diets are low in Mg content (i.e., 30-65% of the RDA for Mg) [26,31-37,39]; most such diets in the USA show that 60-80% of Americans are consuming 185-235 mg/day of Mg [35,40]. In 1900, in contrast, most Americans were consuming 450-550 mg/day of Mg [35]. Low Mg content of drinking water, found in areas of soft-water and Mg-poor soil, is associated with high incidences of IHD, atherosclerosis, coronary vasospasm, hypertension, and SCD [23,26,31,34,41-47]. The myocardial level of Mg has consistently been observed to be lower in subjects dying from IHD and SCD in soft-water areas than those subjects living in hard-water areas [22-24,26,27,31,34,35]. More than 45 years ago, two of us demonstrated that Mg^{2+} behaves as a natural calcium channel blocker in both cardiac and vascular smooth muscle (VSM) cells [24,48-52]. We also showed in experimental animals that Mg behaves as a natural statin in that it can lower cholesterol and triglyceride levels as well as act as a powerful vasodilator in the microcirculation, on coronary arteries and as a cardiac muscle relaxant [24,31,35,47,51,53-57]. Hypermagnesemic diets have been shown to ameliorate hypertension and atherogenesis [24-28,31,33-36,47,58-61].

Using sensitive and newly-designed specific Mg^{2+}-ion selective electrodes, our laboratories demonstrated that patients with alcohol -intoxication, hypertension, IHD, cardiac failure, ischemic and hemorrhagic strokes, alcohol-induced strokes, diabetes types 1 and 2, gestational diabetes, renal -induced vascular changes(associated with elevated cholesterol or chronic alcohol ingestion), preeclampsia, sickle cell anemia in children (and adults), and atherosclerosis exhibit significant reductions in serum/plasma/ whole blood levels of ionized, but not necessarily total, blood levels of Mg [31,35-37,62-83]. Our group has also shown that dietary deficiencies of Mg in rabbits and rats causes vascular remodeling (i.e., arteriolar wall hypertrophy and alterations in the matrices of the vascular walls) concomitant with atherogenesis , high blood pressure, and microvascular vessel vasospasm [25,53,84,85]. These exciting findings have been confirmed, essentially, by other investigators [59,86,87].

Low (Mg^{2+}) Environments or The Presence of Alcohol Result in Concentration -dependent Coronary Arterial Vasoconstriction and Increased Vascular Reactivity: Potential Significance to Alcohol-induced AF

Approximately 40 years ago, our group found that declining levels of extracellular Mg^{2+} ($[Mg^{2+}]_0$) resulted in concentration-dependent constriction and vasospasm of small (< 100 um in diameter), medium and large coronary arteries excised from dogs, sheep, baboons and rats [22-24,49,50,88-94]. These low $(Mg^{2+})_0$-induced vasospasms could only be attenuated or inhibited with elevated concentrations of Mg^{2+} . In addition, we noted that low $(Mg^{2+})_0$ levels enhanced vasoconstrictor responses to a variety of vasoactive and neurohumoral putative transmitters (i.e. , angiotensin II, serotonin, norepinephrine, etc.). We suggested, at that time, that low dietary levels of Mg could result in arrhythmias, IHD and SCD [22-24]. Ever since these early findings were published, a number of clinical studies have been published which support our hypothesis [95-99]. Using perfused, working rat hearts, and *in-vivo* studies, we found that low levels of Mg^{2+} result in reductions in coronary flows, reductions in cardiac output, reductions in stroke volume and peak systolic pressure development, reductions in myocardial intracellular Mg^{2+} levels, reduction in myocardial levels of ATP, increased levels of inorganic phosphate, acidification of atrial and ventricular myocytes, Ca^{2+} overload, and generation of powerful reactive oxygen and nitrogen species [100-104]. Taken together, such results, in themselves, could account in large measure for alcohol-induced AF since ethanol reduces blood and intracellular levels of Mg^{2+}. But, added to this are the physiological, pharmacological and biochemical effects of ethanol on the various chambers of the heart.

Forty years ago, two of us reported that ethanol exerted powerful contractile actions on several types of isolated mammalian arteries [105-110]. Several years later, we found that ethanol could cause similar vasoconstrictor effects on the microscopic blood vessels of living animals using high, quantitative TV image -intensification [65,111-120]. Moreover, two of us reported that ethanol causes concentration-dependent constriction and vasospasm of a variety of small, medium, and large coronary arteries excised from dogs, rats, sheep piglets, and sub-human primates, similar to the actions of low $[Mg^{2+}]_0$ (vide supra) [111-120]. In addition, we found that these actions were associated with rapidly-induced reductions in intracellular levels of Mg^{2+} coupled to increased intracellular levels of calcium($[Ca^{2+}]_i$) [105,110,112,115-120]. Moreover, like low $(Mg^{2+})_0$ perfusion of working rat hearts, we have reported that perfusion of isolated working rat hearts with increasing concentrations of ethanol caused decreased cardiac contractility, decreasing perfusion pressures, decreased coronary flows, decreased levels of myocardial ATP, rise of myocyte inorganic phosphate, acidification of the myocytes, and production of reactive oxygen and nitrogen species [65,102,117,119,120,121]. Such coronary arterial vascular and cardiac myocyte actions of alcohol (in the presence of low Mg^{2+} caused by imbibing ethanol) could certainly account for most of the observed AF, IHD, and SCD. However, these contentions must also be viewed in relation to other recent reports on sphingolipid metabolism (see below) and actions from release of platelet-activating factor (PAF) discussed below.

Low Mg^{2+} or Ingestion of Alcohol Induces Leukocyte Sticking , Increased Adhesivess to Venular Endothelial Walls, Increased Postcapillary Permeability and Vasoconstriction in the Microcirculation: Relation to Inflammatory Reactions and Potential Role in Alcohol-induced AF

Approximately 40 years ago, Ross et al. advanced the hypothesis that atherosclerosis is an inflammatory disease brought about by injury to the endothelial surfaces of macro-and microcirculations [121], for summary of their hypothesis. The hypothesis stated that different forms of injury(e.g., ischemic events) will result in numerous dysfunctions in the homeostatic properties of the endothelium, e.g., increase in adhesiveness of leukocytes and/or platelets, alteration in the procoagulant properties, formation/release of cytokines/chemokines and growth factors. Usually, inflammation is defined as a response

of microcirculatory blood vessels and the tissues they perfuse to infections and damaged tissues which bring cells and host-defense factors/molecules directly from the circulation to all the diverse sites where they are required, in order to eliminate/degrade the offending agents [122,123]. The mediators of the defense mechanisms include white blood cells, phagocytic leukocytes, antibodies, and chemokines and complement proteins [122,123]. The inflammatory process brings these cells and molecules to the damaged or necrotic tissues. During the normal inflammatory process, leukocytes, macrophages, and monocytes migrate across the venous capillary walls through the endothelium due to increases in permeability and move to the site(s) of injury via chemotaxis. The normal mediators for these processes to take place are: adhesion molecules; and cytokines and chemokines. Interestingly, we have found in diverse microcirculatory beds of rats and mice fed either low dietary Mg intake or doses of ethanol (consistent with what is found among heavy drinkers of alcoholic spirits and beer) increased adhesiveness of leukocytes, monocytes and platelets to the venular walls coupled with vasoconstriction and increased postcapillary venular permeability; obviously these phenomena are clear signs of inflammatory responses [14,25,31,35,53,65,115,125-132]. Toll-like receptor -mediated (TLRM) pathways appear to be activated in both the MgD and alcoholic animals. Interestingly, these TLRM pathways are activated through nuclear factor-kappa B (NF-kB) which we have found to be activated very early in MgD and feeding of ethanol [65,115,125-136]. In addition to these microcirculatory reactions, we have found that low dietary Mg intake or ingestion of heavy doses of ethanol result in elevated blood levels of cytokines and chemokines [132], hallmarks of inflammatory reactions. Clearly, such reactions in the atria would perforce, in themselves, result in AF.

Mg^{2+} Regulates Sphingolipid Pathways in Cardiac and Vascular Smooth Muscle Cells: Potential Impact on Alcohol-induced AF

Mg^{2+} depletion has long been known to result in calcium overload in cardiac and VSM cells , including all types of coronary arteries that have been investigated [24,31,34-36,47-52,65,72,85,88,92,93,104,131]. Moreover Mg^{2+} can act as a natural Ca^{2+} channel blocker. Recent studies indicate that Mg^{2+} can modulate sphingolipid pathways in both cardiac and VSM cells [32,35,132]. Ceramides are sphingolipids known to be released as a consequence of sphingomyelinses (SMases) acting on sphingomyelin (SM), a component of all cell membranes, or as a consequence of the activation of serine palmitoyl transferase 1 and 2 (SPT 1 and SPT 2) (a synthetic pathway) [132,137-146]. Ceramides are now thought to play important roles in fundamental processes such as inflammation, angiogenesis, membrane-receptor functions, cell proliferation, microcirculatory functions, cell adhesion, immunogenic responses, excitation-contraction coupling events in cardiac and VSM cells, and cell death (i.e., apoptosis) [31,35,134,135,143,144,146-151]. SPT 1 and SPT 2 are the rate-limiting enzymes in the biosynthesis of sphingolipids [146]. An upregulation of SPT 1 and 2 has been hypothesized to play an important role in apoptosis cell death events taking place in atherogenesis [136,153]. Such upregulation could be quite pivotal in producing plaques on the endothelium of coronary vessels leading to ischemia and AF. Working with perfused rat hearts, we have noted incremental rises in ceramides as the $(Mg^{2+})_0$ was reduced concomitant with decreases in stroke volume, increased levels of lactic acid dehydrogenase and creatine phosphokinase, increased lipid peroxidation of cardiac muscle cells, reductions in myocardial intracellular pH, and generation of ROS [100-104,139,142,144,152]. We have noted almost parallel effects of rising concentrations of ethanol on the identical ceramide, physiological and biochemical parameters in perfused working rat hearts [102,115,117,121].

It is of considerable interest to note, here, that, experimentally, myocardial infarctions have been shown to be associated with rising levels of ceramides [155-157]. In human subjects, it has been reported that stable angina pectoris, unstable angina pectoris, and acute myocardial infarction is also associated with rising levels of ceramides [156,157]. In some of these patients, a clear elevation in SMases was observed.

Binge-drinking, and alcohol withdrawal, which is very common among young adults, has been reported in murine animal experiments, to produce marked changes in ceramide regulatory genes along with metabolic products and reductions in SM in mouse brains [166,167]. In addition, apoptotic cell death of neuronal cells induced by ethanol is associated with rising levels of ceramide. As the heart's chambers, including the atria, are normally under baroreceptor and sympathetic neural control mechanisms, generation of ceramides in heavy alcohol drinkers certainly could be expected to produce arrhythmias. We propose that the ethanol-induced reduction in blood, coronary and myocardial levels of Mg^{2+} would set into motion the generation and release of ceramides. This, taken together with the direct effects of low $(Mg^{2+})_0$ and ethanol, would result in AF.

During the performance of our foregoing *in-vitro* and *in-vivo* studies, using proton -nuclear magnetic resonance spectroscopy, we noted rapid formation of platelet-activating factor (PAF) and PAF-like lipid molecules [133].

Mg^{2+}- Deficient Environments or Rising Concentrations of Alcohol Lead to Formation of PAF : Potential Significance to Atrial Fibrillatory Events

PAF is now known to play major roles in inflammatory responses and atherogenesis [168-170]. In addition, PAF is known to affect the heart and cardiac muscle cells in numerous ways [168-170]. For example, PAF can produce coronary arterial vasoconstriction, lower 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 muscle chronotropicity and membrane action potentials, as well as alter potassium currents in isolated cardiomyocytes [132,169,170]. All of these attributes of PAF's actions on the myocardium and coronary vascular tree would be more than enough to cause profound atrial fibrillation. Moreover, a variety of the circulating blood formed elements (e.g., polymorph nuclear leukocytes, platelets, basophils, and macrophages can elaborate PAF [133,171,172]. Recently, we have found that coronary, cerebral, and aortic VSM cells can also elaborate and release PAF [132]. A number of investigators employing intravital microscopy techniques, similar to those used in our laboratories [132] have demonstrated that PAF increased the number of white blood cells in the microvessels concomitant with intense vasoconstriction-spasms with increasing concentrations of the putative lipid mediator (i.e., PAF), less leukocyte rolling, and increased adherence of the leukocytes to the endothelial surfaces with increased venular-postcapillary permeability [132]. Interestingly, we have reported that ceramides can produce almost similar phenomena in a variety of microvascular beds when studied by high-resolution video microscopy [35,132,171]. We believe, rather firmly, that these older and newer experimental studies could be used to advance our hypothesis that generation and release of both PAF and ceramides due, in large measure, to ethanol's effect on lowering Mg^{2+} resulting in MgD states are more than likely involved in generation of

alcohol-induced AF.

Potential Reasons for Why Women are Much Less Susceptible to Alcohol-induced AF

As stated above, prior to menopause, women demonstrate one-third the rate of alcohol-induced AF, hypertension and SCD [10,11] We believe this may be due, mainly, to the ability of female cardiac VSM and endothelial cells , in the presence of estrogenic hormones, to be in a better position to retain more intracellular Mg^{2+} in these cell types. Several years ago, we showed, using diverse types of isolated VSM and endothelial cells in primary cultures that estrogenic hormones controlled the concentration of intracellular Mg^{2+} levels [158,159]. Studying women, prior to menopause, we found that the blood levels of ionized Mg are controlled by the ratio of estrogenic hormones to progestational hormones [160-164]. Obviously, having these pieces of cellular and blood level data, one could conclude that since women , prior to menopause, in the presence of estrogenic hormones, could be expected to retain critically-important levels of Mg^{2+}, thus making it more difficult for consumption of alcoholic beverages to cause AF in these younger women. We believe this hypothesis can be easily tested in premenopausal vs. menopausal women.

Importance of Mg Supplemented Drinking Water and Beverages for Prevention and Amelioration of Alcohol-induced AF

Over the past 25 years, our laboratories have been investigating the utility of Mg-supplemented or naturally-occurring spring waters to avoid the pitfalls of dietary-and/or metabolically-induced MgD-states which affect heart health [31,35,65,104,132, 135-137, 139-142]. Our results, to date, bolster the idea that water intake (e.g., from tap waters, well waters, bottled waters, beverages using tap/well/spring waters, or desalinated waters) in humans should contain at least 25-40 mg/liter/day of Mg^{2+} [173]. A number of experiments done in our labs indicate that most , if not all of the cardiovascular manifestations (i.e., decreased cardiac output, decreased coronary flows, decreased myocardial contractility, lipid peroxidation of cardiac muscle membranes, synthesis/release of toxic ceramides, PAF, cytokines and chemokines, mitochondrial release of cytochrome C, increased Ca^{2+} entry and overload, myocardial acidification, loss of cardiac ATP levels, apoptosis, etc.) observed in hearts of experimental animals fed low dietary Mg, or given elevated ingestion of ethanol, can be prevented or ameliorated when imbibing drinking waters with appropriate amounts of Mg^{2+} [131,132,135-137,139-142]. We are convinced the latter inclusion in our diets should go a long-way towards the prevention and amelioration of atrial arrhythmias, supraventricular arrhythmias, and cardiac ischemic events in both "binge-drinkers" and people who ingest too much alcohol. Interestingly, on the basis of our work in animals , the World Health Organization has suggested people should consume drinking waters containing our recommended 25-40 mg/liter/day of Mg^{2+} [172,173]. It is our hope that two large scale clinical trial studies , one on "binge-drinkers", and one with people who consume heavy doses of ethanol, can be instituted to test our hypothesis.

Conclusion

Although the exact cause(s) of an increased incidence of alcohol-induced atrial fibrillation in heavy -drinkers and "binge-drinkers" is not known, Mg^{2+} depletion is clearly observed in all patients when looked-for. Experimentally, heavy ingestion of alcoholic beverages leads to AF, cardiac ischemia, decreases in cardiac output and contractility, losses in myocardial ATP, generation of reactive oxygen species, loss of myocardial intracellular Mg^{2+}, myocardial Ca^{2+} overload, generation of ceramides and PAF, increased blood and myocardial cell cytokines and chemokine's) coupled to inflammation-like events in the microcirculation. At least in experimental animals, elevated dietary levels of Mg^{2+} can overcome or ameliorate most of these effects of ethanol on the heart. We suggest that all human drinking waters contain at least 25-40 mg/liter/ day of Mg^{2+} as a preventive against alcohol-induced AF, supraventricular arrhythmias, and ischemic events.

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