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SciFed Journal of Addiction and Therapy

Review Article Open Access

Magnesium Decreases Alcohol-induced Brain Damage and Prevents Experimentally-induced Strokes: Roles of Ceramides and Platelet-Activating Factor and Potential Implications for Human Subjects with Alcohol-induced Dementia

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Of all drugs, alcohol (i.e. ethanol) is the most abused drug and is responsible for countless deaths and hospitalizations worldwide each year. In the USA, alone, excessive alcohol drinking accounts for about 10,000 deaths per year. Alcohol drinking is a major risk factor for irreversible brain damage and strokes. Excessive drinking over years results, in a high-degree of dementia in human subjects. Alcoholic-induced dementia is very similar to Alzheimer's disease. It results in poor-judgment, confusion, decreased cognitive abilities, and memory loss. One of the major effects of heavy alcohol drinking and alcohol-induced dementia is development of what has been termed, the "Wernicke-Korsakoff syndrome". In this syndrome, the patient presents with "Korsakoff psychoses", causing hallucinations, thought by some to be a consequence of thiamine deficiency. But, this cause is disputed by many investigators.

Of the many minerals in the body that is most affected by alcohol drinking, it is magnesium (Mg). Although numerous drugs can deplete the body's tissues and cells of Mg, ethanol is the greatest depletory of Mg [1-6]. It also is the number-one drug which can reduce intracellular levels of free , ionized Mg (Mg^{2+}) in minutes, particularly in cerebral brain cells (e.g. astrocytes, endothelial cells, vascular smooth muscle cells , and all types of neurons studied to date) [4-15].

Alcohol abuse leads to primary malnutrition that is a 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 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. Serum hypomagnesaemia occurs in from 30 to 60% of the alcoholic population [1-6]. Nearly 90% of patients undergoing alcohol withdrawal are hypomagnesemic and at high-risk for strokes and hallucinations.

Overall, looking at many clinical studies, there is a clear relationship between heavy alcohol ingestion (i.e., 3-5 drinks/day), sudden –cardiac death (SCD), and dementia [16-19]. However, very few of these alcohol-induced deaths are ever autopsied, so it is impossible to determine how many of these subjects had severe brain damage and underwent strokes or stroke-like events. Less than 5% of all deaths in the USA ever result in a complete autopsy. From the available data, it is also apparent there is a clear relationship between "binge drinking "and SCD. Again, since autopsies are seldom done, how many of

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Received May 14, 2018; **Accepted** June 19, 2018; **Published** July 02, 2018

Citation: Burton M Altura (2018) Magnesium Decreases Alcohol-induced Brain Damage and Prevents Experimentally-induced Strokes: Roles of Ceramides and Platelet-Activating Factor and Potential Implications for Human Subjects with Alcohol-induced Dementia. SF J Addic Ther 2:1.

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these deaths are related to potential brain damage and stroke-like events? In those subjects that have been autopsied, the only findings often found at "post mortem" are fatty livers of typical alcohol ingestion, often leading pathologists, inaccurately, to term the SCD to alcohol-induced liver toxicity. In many of these victims, pathologists failed to make fine histological sections of key areas of the brain, e.g., medulla oblongata, cerebral hemispheres, pons, hypothalamus, etc., which might have picked-up signs of stroke-like events. "Binge drinking" (more than 80g alcohol ingested in< 24 hrs) can result in intracerebral hemorrhage (ICH), subarachnoid hemorrhage (SAH), and cerebral infarctions. Particularly alarming, are the numbers of reports suggesting that even moderate drinking elevates the risk for ICH and SAH [20-23].

Over the past three decades, evidence has accumulated to indicate that daily dietary deficiency in Mg intake and/or errors in Mg metabolism pose serious risks for development of SCD, coronary artery spasm, myocardial infarction, and brain damage [24-33]. Using perfused, working rat hearts, Ca^{2+}imaging, optical imaging-spectroscopy and ^{31}P-NMR spectroscopy, as well as in-vitro studies, we found that low levels of Mg^{2+} result in reductions in coronary flows, reduction in cardiac output, reductions in stroke volume and peak systolic pressure development, reduction in myocardial intracellular Mg^{2+} levels, reduction in myocardial levels of ATP, increased levels of intracellular inorganic phosphate, acidification of atrial and ventricular myocytes, Ca^{2+} overload, coronary vasospasm, increases in free myoglobin, rises in inorganic phosphate, increases in mitochondrial reduced cytochrome C, and generation of reactive oxygen and nitrogen species [34-38]. Interestingly, we reported very similar results when rat hearts were exposed to increasing concentrations of ethanol, both in-vivo and in-vitro [12, 38, unpublished findings]. Examination of rat and canine brains using ^{31}P-NMR spectroscopy, optical spectroscopy and Ca^{2+}-imaging, which were exposed to increasing doses of alcohol, also resulted in Mg^{2+} deficiency, Ca^{2+} overload, reduction in levels of cellular ATP, increased levels of reduced cytochrome oxidize, increased levels of inorganic phosphate, increased levels of deoxyhemoglobin, acidification of neurons, astrocytes and cerebral vascular smooth muscle cells, and generation of reactive oxygen and nitrogen species in the cerebral cortex , hippocampus, pyramidal cells, and the medulla oblongata [4, 5, 7, 9, 11-13, 20, 34-59, unpublished findings].

Relationship of Mg to Alcohol Intoxication, Cerebral Vascular and Parenchymal Stability, Strokes and Brain Damage

From the foregoing, it is now obvious that drinking of alcohol poses serious risks not only for the heart, but the brain as well. Much of this danger appears to be a consequence of Mg depletion. It has been known for more than 40 years that ingestion of alcoholic beverages results in body depletion of Mg [17, 18]. But, what is so special and important about this mineral, Mg? Mg is a co-factor for more than 500 enzymes in the body, and is the second most abundant intracellular action after potassium. It is vital in numerous physiological, cellular and biochemical reactions including carbohydrate, lipid, protein, DNA and RNA metabolism, among many, many other pathways [26, 60]. Several epidemiological studies in North America and Europe have shown that people consuming Western-type diets are low in Mg content (i.e., 30-60% of Americans are consuming only 185-235 mg/day of Mg [61-64]. In contrast, in 1900, most Americans were consuming 450-550 mg/day of Mg [61]. 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 artery vasospasm, hypertension, strokes, and SCD [24-27, 65-69]. 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 living in hard-water areas [24-27, 61, 65, 70]. It is of considerable interest to note, here, that we have found that strokes in humans, brain trauma (with and without alcohol intoxication) as well as Mg- deficient rats, and alcohol-induced hemorrhagic strokes in rats, all have shown deficits in brain and blood ionized Mg levels [4, 5, 7, 9, 11, 13, 20, 41, 43, 44, 47, 48, 53, 71, 72, unpublished findings]. Vink and his colleagues, in extensive animal and human studies, have also reported that brain trauma and injury resulted in deficits in brain tissue and serum Mg [73, 74]. Removal of hippocampal brain slices from Mg-deficient rats showed deficits in neuronal cell Mg, elevated Ca^{2+}, reduced ATP, and elevated inorganic phosphate [unpublished findings]. Interestingly, headaches (including many induced by alcohol ingestion) of all types in both adult humans and children have been found to exhibit deficits in serum ionized Mg levels and are often treatable with administration of only Mg [75-79].

More than 45 years ago, two of us demonstrated that Mg^{2+} behaves as a natural calcium channel blocker in cardiac, vascular, endothelial, and cerebral vascular muscle cells as well as in hippocampal-pyramidal brain cells [61,

80-92]. We also showed in experimental animals, and human subjects (with type 1 and type 2 diabetes mellitus), that Mg behaves as a natural statin in that it lowers serum levels of cholesterol, triglycerides and LDL , as well act as a powerful vasodilator in the microcirculation and on coronary and cerebral arteries, and as a cardiac muscle relaxant [61, 93-105]. In contrast, hypomagnesemic blood levels have been shown to ameliorate hypertension, atherogenesis, atrial arrhythmias, headaches of all types, and alcohol-induced strokes as well as increase cerebral blood flow and limit cerebral tissue damage from alcohol intoxication [4-6, 11, 31, 41, 43, 44, 53, 55, 60, 61, 70, 75-79, 93, 94, 100, 106-118].

With the use of sensitive and newly-designed specific Mg^{2+}-ion selective electrodes, our laboratories have shown that patients with alcohol intoxication, IHD, cardiac failure, ischemic and hemorrhagic strokes , diabetes types I and II, renal-induced vascular pathology, preeclampsia, and atherosclerosis exhibit significant reductions in plasma, serum/ whole blood levels of Mg^{2+} [5, 7, 11, 20, 44, 47, 48, 61, 70-72, 76-79, 93, 94, 105, 117, 119-128]. Our group has also found that experimentally-induced dietary deficiencies of Mg in rats, rabbits and mice causes vascular remodeling (i.e., arteriolar wall hypertrophy and alterations in the matrices of the vascular walls) in the brain, skeletal muscle, and splanchnic microcirculations concomitant with atherogenesis, high blood pressure, and microvascular vasospasm [26, 27, 37, 70, 84, 100, 106, 129].

Low $[Mg^{2+}]_0$ Environments or The Presence of Increasing Concentrations of Alcohol Result in Concentration-dependent Cerebral Arterial, Venular and Arteriolar Vasoconstriction as Well as Increased Vascular Reactivity, Inflammatory Responses and Formation of Reactive Oxygen Species (ROS): Relevance to Alcohol-induced Leukocyte -Endothelial Interactions in Microcirculation, Apoptosis, Necroptosis and Ferroptosis

Almost 50 years ago, our group reported that declining levels of extracellular Mg^{2+}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 [26, 80-88, 95, 96, 98, 122]. Similar results were found by our group using small, medium, and large cerebral and middle cerebral vessels excised from dogs, sheep, baboons and rats [20, 61, 82, 86, 87, 88, 96, 87, 98]. These low $[Mg^{2+}]_0$ -induced vasospasms could only be attenuated or inhibited with elevated concentrations of Mg^{2+}. Further studies showed that administration of ethanol can induce similar responses on isolated cerebral vessels (from the same diverse mammals) as well as on the intact brain microcirculatory arterioles and is associated with rapidly-induced reductions in cellular $[Mg^{2+}]_I$ coupled to movements and release of calcium ions into the vascular smooth muscle and parenchymal brain tissues [4, 7, 9, 11, 20, 39, 40-44, 53, 55, 57, 83]. Moreover, these low $[Mg^{2+}]_0$ levels enhanced vasoconstrictor responses to a variety of vasoactive and neurohumoral putative neurotransmitters (e.g., angiotensin II, serotonin, numerous vasoactive peptides, etc.). We suggested, at that time, that low dietary levels of Mg and alcohol intoxication could result in cellular calcium overload, mitochondrial dysfunction, disturbances in Ca^{2+} and K^+ currents in brain capillary endothelial cells, arrhythmias, fibrillation, IHD, SCD, strokes and brain damage [4, 7, 11, 13, 20, 39-45, 48-56, 91, 92, 117].

On further investigation, we found that both ethanol and low $[Mg^{2+}]_0$ induced generation of ROS (e.g., H_2O_2, hydroxyl radicals, ferrylmyoglobin, NO, peroxynitrite radicals as well as hypochloric acid) in the heart and on brain blood vessels [4, 5, 7, 11, 15, 36, 37, 43, 48, 53, 54, 56, 58, 61, 70, 117, 129-138, unpublished findings]. Studying the in-situ brain microcirculation with high power (up to 3,200 x –magnification) TV-image intensification microscopy of the post-capillary venules, we noted that Mg-deficient animals or animals given increasing doses of ethanol, demonstrated rolling and adherence of leukocytes on the endothelial walls with eventual infiltration of leukocytes and macrophages across the venular walls into the brain parenchymal tissues and increased myeloperoxidase staining, suggesting clear inflammatory responses with generation of peroxidase, H_2O_2, and hypochloride free radicals [4, 5, 7, 11, 43, 48, 56, 57, 59, unpublished findings].

Using a host of biochemical and molecular assays, we found that Mg deficiency (in intact animals, or primary cultured cerebral vascular smooth muscle cells), or prolonged culture of these cells with ethanol, showed clear signs of three types of cell death, i.e., apoptosis, necroptosis and ferroptosis [129, 139, 140, unpublished findings].

Use of ^{31}P-Nuclear Magnetic Resonance Spectroscopy (^{31}P-NMRS) in Animals Given Stroke-like Doses of Alcohol Results in Brain Declines in ATP, $[Mg^{2+}]_I$, and Phosphocreatine with Rises in Levels of Inorganic Phosphate and N-Acetylaspartate

In-vivo studies performed by our group, using intact rats and high-powered ^{31}P-nuclear magnetic resonance spectroscopy (^{31}P-NMR) to probe the intact brain, have found that increasing concentrations of ethanol resulted in rapid alterations in brain biochemistry and neurophysiology [4, 7, 9, 11, 13, 20, 44, 46, 48, 53]. We found that diverse brain cells demonstrated declines in intracellular free [Mg], rapid declines in neuronal ATP and ADP, declines in brain phosphocreatine, acidification (i.e., decreased neuronal pH), concomitant with rises of intracellular free inorganic phosphate and N- acetylaspartate, all signs of dying and/or compromised brain neuronal cells and parenchymal tissues [4, 5, 7, 9, 11, 13, 44, 48, 53, unpublished findings]. Working with primary cultured canine and baboon cerebral vascular smooth muscle cells, primary cultured rat brain astrocytes and rat brain hippocampal brain slices, we have found very similar biochemical and molecular alterations [4, 8, 10, 14, 20, 41, 44, 53]. In addition, we noted that these diverse cells demonstrated rises in $[Ca^{2+}]_I$ concomitant with reductions in intracellular pH (i.e., intracellular acidification) and rises in inorganic phosphate levels [4, 8, 11, 42, 43, 52, 53, unpublished findings]. Moreover, ethanol exposure resulted in lipid peroxidation and activation of nuclear factor – kB [58, 59]. But, what is causing these detrimental alterations in brain biochemistry? Is it the alcohol, per se, as some investigators believe or is it some intermediate(s) molecule (s)? Using proton -NMR spectroscopy, about 20 years ago, in preliminary experiments, we noted that cerebral vascular smooth muscle cells, exposed to increasing concentrations of ethanol demonstrated rises in the sphingolipid, ceramide, and what looked like rising levels of platelet-activating factor (PAF) and PAF-like lipids [131, unpublished findings].

Roles of Ceramide, PAF and PAF-like Lipids in Alcohol-induced Strokes and Brain Damage

Ceramides are now thought to play important roles in fundamental cellular, biochemical and physiological processes such as cell proliferation, membrane-receptor functions, oxidative stress, angiogenesis, diverse microcirculatory functions, immune-inflammatory functions, cell adhesion, activation of nitric oxide synthases, alterations in membrane lipid domains, and programmed cell death, among other functions. We have reported, previously, that low extracellular Mg levels cause mitochondrial alterations, programmed cell death(discussed above), activate nitric oxide synthases, oxidative stress, and activation of all five of the major enzymes in the sphingolipid pathway leading to synthesis/release of ceramides [4, 130-133].

PAF is known to play major roles in both inflammatory reactions and atherogenesis. A variety of the circulating blood-formed elements (e.g., polymorphonuclear leukocytes, platelets, basophils, and macrophages) as well as endothelial cells can elaborate PAF. Interestingly, all of these cell types play roles in hemorrhagic and ischemic strokes. We have shown, recently, that cerebral vascular smooth muscle cells, astrocytes, brain capillary endothelial cells, and hippocampal brain slices all can elaborate PAF in low Mg^{2+}environments [141, 142, unpublished experiments].

Since preliminary studies, using isolated canine and baboon arteries, suggested that exposure of these tissues to ethanol and low Mg^{2+} resulted in increased levels of the sphingolipid, ceramide, and PAF, we proceeded to examine primary canine, rat, and baboon cerebral vascular smooth muscle cells exposed to increasing concentrations of ethanol. These cells demonstrated, as expected, rising levels of ceramide and PAF [142, unpubished findings]. In addition, we found that ethanol resulted in activation of N-sphingomyelinase and acid-sphingomyelinase concomitant with increasing reductions in free [Mg] [142, unpublished findings]. Preliminary studies seem to indicate that agents that inhibit the synthesis of PAF will inhibit accumulation of ceramide and PAF [141]; surprisingly, PAF inhibitors also seemed to markedly attenuate the ability of ethanol to reduce intracellular levels of [Mg] [143]. Whether or not sphingolipids and PAF are critical molecules in the stroke and brain-damaging effects of ethanol will have to await further investigation.

Conclusion

Although the current focus among physicians and the public seems to be the increasing number of deaths, particularly among the youth, on “overdosing by opioids”. The most abused drug, among the youth and college students, is “alcohol”. Alcohol intoxication and abuse accounts for countless deaths worldwide, particularly in the USA and

Russia. Death certificates usually list these deaths as from hepatic and respiratory failure. Unfortunately, very few complete autopsies are ever performed on these victims. Importantly, repeated ingestion of alcohol, over many years, often results in dementia, Wiernicke-Korsakoff syndrome and hallucinations. We review data and studies, herein, which suggest, rather strongly, that many of these alcohol-induced deaths are caused by brain damage (to vital areas) and hemorrhagic and ischemic strokes. Numerous experiments performed by our group on diverse mammals, using intact brains, isolated cerebral vascular, neuronal, astrocytic, and endothelial cells point to an important, overlooked role of magnesium in the responses of the brain to alcohol. Our studies on human subjects and animals demonstrate that alcohol causes rapid depletion of free, intracellular Mg ions coupled to loss of ATP, ADP, and phosphocreatine along with rises in cellular acidification, free inorganic phosphate, and N-acetylaspartate, all clear signs of either impending brain- cell death or necrosis of cells. Very recent experiments point to important roles for sphingolipids (e.g., ceramide) and platelet-activating factor (PAF) and other PAF-like lipids in the brain's responses to alcohol. Collectively, such clinical and experimental studies point to the need for complete autopsies in alcohol-induced deaths in order to determine whether the deaths were caused by strokes or increasing brain damage over time. Our newer studies on sphingolipids and PAF point to the need for such studies in humans known to be alcohol-abusers. We believe if the latter demonstrates proof for the key-involvement of sphingolipids and PAF, drugs could be designed to help alcohol-abusers and prevent brain damage, alcohol-induced dementia, Wiernicke-Korsaff syndrome, and probably prevent induction of strokes.

Acknowledgements

Some of the original experimental and clinical studies mentioned in the above were supported, in part, by research grants from The N.I.H. (National Institute on Alcoholism and Alcohol Abuse, The National Institute on Mental Health, and The National Institute on Drug Abuse to B.M.A. and B.T.A.). We also received unrestricted grant support from several pharmaceutical companies including CIBA-GEIGY, SANDOZ, and Bayer.

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Citation: Burton M Altura (2018) Magnesium Decreases Alcohol-induced Brain Damage and Prevents Experimentally-induced Strokes: Roles of Ceramides and Platelet-Activating Factor and Potential Implications for Human Subjects with Alcohol-induced Dementia. SF J Addic Ther 2:1.