

Stroke, Headaches and Hallucinations: Real Dangers of the Recreational Use of Amphetamines and Ecstasy-Like Drugs: Unrecognized Role of Hypomagnesemia

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Abstract

During World War II, amphetamines became widely used among US Army troops to increase wakefulness, improve morale, and cut-down on fatigue [1,2]. In the 1950's, physicians started to prescribe amphetamines often in a haphazard fashion [3]. As of the past 10 years, it is said that there are now at least 50 million users of amphetamines in the USA alone. The use of amphetamines is thought to increase the risk of having a stroke by 4-5-fold over non-users [4,5]. Although amphetamines, pharmacologically, behave in many respects like sympathomimetic agents, this attribute does not explain why these drugs, particularly methamphetamines, pose a great risk for both hemorrhagic and ischemic strokes (IS) [4,5]. In addition to their actions on the brain, amphetamines and methamphetamine pose great risks for cardiomyopathy, reductions in left ventricular ejection fractions and left atrial volumes, resulting in arrhythmias, pulmonary dysfunctions, and thromboses leading, often, to embolic strokes [3-5]. Moreover, the illicit use of amphetamines is usually accompanied by intense headaches of unknown origin [3-5].

Keywords: Stroke; Headaches; Hallucinations; Amphetamines; Hypomagnesemia

Introduction

Another pathophysiological manifestation of amphetamine (AM) and methamphetamine (METH) use is that these drugs cause very high increases in arterial systolic and diastolic blood pressure which is thought to contribute to stroke induction [3-5]. But, how do these spikes in blood pressure produce both hemorrhagic and ischemic strokes? Explanations for these different types of strokes are difficult to explain only in terms of blood pressure elevations. Autopsies of AM and METH stroke victims have revealed blood vessel injuries in the brain along with vasculitis, necrosis, and what looks like arterial vasospasm [3-5]. Among the youth (e.g. people < 45 years old), a single intravenous dose in a first-time user has been documented to induce a stroke, thus making these agents extremely dangerous [3-5]. Unfortunately, with the current emphasis on deaths from fentanyl, this danger has not been brought to the attention of the uninformed public. Moreover, hospitalizations due to abuse of AM and METH are costing the healthcare systems in the USA, UK, Europe and Russia billions of dollars per year which is overwhelming the healthcare systems here and abroad.

Amphetamines, illicit drugs and induction of strokes

Since the advent of home-made laboratories, it has been easy to manufacture/synthesize "designer drugs" derived from amphetamines such as "Ecstasy" which in many respects resembles hallucinogenic/psychedelic drugs like mescaline, psilocybin, and peyote, thus causing

combined sympathomimetic and hallucinogenic effects, thus producing potentially very dangerous effects on our youth. The majority of the “Ecstasy” in use is 3,4-methylenedioxymeth-amphetamine (or MDMA), N-ethyl-3,4-methylenedioxyamphetamine (or MDEA), or 3,4-methylenedioxyamphetamine (or MDA). Current evidence indicates that illicit synthesis of all three of these drugs is producing an increase in their use, vastly, among college students [6]. The porous Southern border of the USA has made it relatively easy for drug traffickers from Mexico and Central America to bring huge quantities of AM, MDMA, MDEA and MDA into the USA at cheap prices.

Although alcohol and marijuana, which also can induce strokes [3-5,7-11], are the most abused drugs in the Western world, amphetamines and Ecstasy-like designer drugs are a close third in abuse, particularly among the youth. Why young women are more susceptible to AM and METH-induced strokes than men is not known, but has been speculated to be related to oral contraceptive use. Overall, the number of deaths and hospitalizations from AM and METH abuse, when added to those deaths from fentanyl abuse, combine for the third leading cause of death in the USA.

Below, we point out a number of clinical and experimental studies, mostly overlooked, including our own studies, which provide considerable evidence supporting a role for AM, METH and Ecstasy-like drugs as causal factors in both IS and hemorrhagic strokes. We also provide new evidence for, what we believe are the underlying biochemical and molecular pathways by which these drugs probably produce IS and hemorrhagic strokes.

It is a wide-perception that ingestion, smoking, intravenous injection, or snorting amphetamines is completely safe. Unfortunately, this perception appears to be wide-spread among the youth (e.g. children below the age of 18). However, more than 70 years ago, it was first reported that ingestion of amphetamine produced a stroke (i.e. subarachnoid and subdural hemorrhages), followed by death, in a 36- year-old man [12]. Over the intervening years, up to the present day, there have been multiple documentations of both IS and hemorrhagic strokes in both men and women induced by AM and METH [3-5,13,14]. Based on these reports, the incidence of METH-induced strokes in young people (< 45 years old) varies between 7 - 15% [3-5]. A major problem in pin-pointing the exact incidence of AM and METH-induced strokes is two-fold: 1. often AM or METH are mixed with other drugs (i.e. alcohol, heroin, psychedelics, cocaine, fentanyl, etc.) in order to overcome tolerance; and 2. age and sex appear to confound the incidences. It is, however, clear that the degree(s) of the pharmacological effects of AM, METH, and “Ecstasy”-like drugs vary with the experience of the user, dose, route of administration, and vulnerability of the user to psychoactive stimulants [3-5].

Experimental studies demonstrate amphetamines and derivatives can result in regional vasoconstriction-vasospasm in brain and strokes: Beneficial effects of magnesium

Using anesthetized rats, and exposure of the pial-brain microcirculation, as well as the medullary microvasculature, and the cerebellar microvasculature (by a scrape-down method) [15], we have found that a variety of drugs of abuse (including all hallucinogens so far tested), including alcohol, LSD, heroin, PCP, psilocybin, cocaine, peyote, mescaline, AM, METH and “Ecstasy”, among others produce concentration-dependent vasoconstriction-vasospasm of intact cerebral arterioles, metarterioles, and muscular venules as well as potent dose-dependent contraction of isolated cerebral arteries excised from dogs, rats, and monkeys [11,13-46]. In addition, using high-resolution quantitative video microscopy at magnifications up to 6,500 x-normal), on intact rat brains, we have found that these drugs of abuse, including AM, METH, and “Ecstasy” induce rupture of postcapillary venules with transudation of blood-formed elements, including red blood cells, into the surrounding perivascular tissue spaces [15]. These reactions are clearly representative of both IS and hemorrhagic strokes. Surprisingly, pretreatment of the experimental animals with diverse magnesium (Mg) compounds, given by local, oral or intravenous administration, prevented many of the vasospasms and stroke-like microcirculatory reactions induced by AM, METH and “Ecstasy”-like agents [15]. We confirmed much of these findings through the use of ³¹P-nuclear magnetic resonance spectroscopy (³¹P-NMRS) [35] in the living rat. In addition, in those animals that died, we noticed a precipitous rise in brain cell inorganic phosphorous content which was preceded by reductions in intracellular free Mg concentration ([Mg²⁺]_i) and followed by marked reductions in brain cell ATP levels [15]. We believe this constellation of changes in brain cellular Pi, [Mg²⁺]_i and ATP may prove to be biomarkers of impending doom in human subjects self-administering stroke-like doses of AM, METH or “Ecstasy-like drugs. This suggestion should be investigated in future human studies using ³¹P-NMRS.

Using new technology to implant electrodes in the hippocampus of the freely moving rat, we found that alcohol and other drugs of abuse suppressed the firing of numerous pyramidal neurons in a dose-dependent manner [42]. We believe if such data are confirmed, in humans, this would suggest a reasonable rationale for why permanent disturbances of memory and cognitive functions are observed after chronic administration of AM, METH and Ecstasy. Such effects could portend potential, irreversible damage to deep areas in the brain like the hippocampus.

Potential role of vasospasm and hypomagnesemia in AM, METH and ecstasy-induced euphoria, headaches and hallucinatory actions

Euphoria is an affective state and a form of pleasure that goes back to biblical times. It makes a person experience intense forms of well-being, happiness, and often ecstasy. It has often been suggested that euphoria induced by alcohol, psychoactive stimulants (such as AM, METH and Ecstasy), designer drugs, LSD, PCP, heroin, etc., occurs via stimulation of hedonic hotspots within the brain's overall reward system [47]. Interestingly, asphyxiation initially produces an intense feeling of euphoria, often leading people to intentionally induce asphyxiation and erotic sensations (e.g. brief periods of hypoxia). Our findings of reversible /irreversible AM-, METH- and ecstasy-induced vasospasms of microvessels in the cerebellum and medulla, of living rat brains [15], would be enough to curtail blood flow in the brain to the point that key neurons, glial cells, and astrocytes do not get enough oxygen to function properly. We suggest, like that seen in pilots at high altitude (> 15,000 feet) in non-pressurized cabins, in World War II, who experienced a euphoric sense of well-being, ingestion, or snorting AM, METH, or Ecstasy-like drugs will reversibly induce vasoconstriction and vasospasm of the cerebellar and medullary microvessels (most likely hippocampal microvessels as well), thus producing oxygen-lack and temporary light-headedness and euphoria. We believe that AM, METH, and Ecstasy-like drugs -induced reductions in intracellular free, ionized Mg and ATP together with intracellular rises in inorganic phosphorus and free calcium ions, discussed above, would help to trigger the latter events.

The headache-effects of the amphetamines, alcohol, cocaine, marijuana and numerous illicit drugs mentioned, herein, could also be explained, in large measure, by a reversible cerebral vasoconstriction/vasospasm syndrome we first proposed for migraine headaches in 1981 [38] caused by reduction of brain intracellular Mg and increased brain intracellular levels of calcium ions [for reviews, see 10,48]. Through examination of approximately 4,000 migraine headache patients, we have found that 90% of those that demonstrated significantly lowered levels of serum ionized Mg levels, including those with cluster and tension-type headaches, had their headache pains and photophobia alleviated by a single intravenous injection of $MgSO_4$ [49-59]. We believe these results may have direct application to the various types of headaches observed in humans imbibing AM, METH and Ecstasy. Whether intravenous injections of $MgSO_4$ will alleviate the neuropathic pain observed in subjects taking AM, METH and Ecstasy or other illicit drugs remains to be tested.

Importance of Mg to body homeostasis, cell normalcy and pathophysiology

Low Mg content of drinking waters found in areas of soft-water and Mg-poor soil, is associated with high incidences of ischemic heart disease (IHD), atherosclerosis, coronary and cerebral arterial vasospasm, hypertension, and strokes [60-64]. In this context, it is vital to point out, here, that our group has found that strokes in humans (with and without PCP, psilocybin, mescaline, peyote extracts, cocaine, marijuana, alcohol, or polydrug use) all have shown deficits in blood ionized Mg levels [9-11,15,32-34,36,37,40,41,43,44,46,58,64, unpublished findings]. Our findings on humans high on AM, METH or Ecstasy (coming into the ERs of our hospitals) exhibit similar characteristics on demonstrating significantly lowered blood ionized Mg levels [unpublished findings]. Such drug-induced low, blood ionized Mg levels result in calcium overload in cerebral vascular smooth muscle cells (VSMC) and glial cells in primary culture, as well as in red blood cells (using ^{31}P -NMRS to measure free Mg^{2+}), as we have shown in IS and hemorrhagic strokes. This calcium overload results in death of neurons, glial cells, endothelial cells, dendritic cells, and VSMC via apoptosis and necroptosis [unpublished findings].

Mg is a co-factor for more than 500 enzymes [59] and is the second most abundant intracellular cation after potassium. It is critical in numerous physiological, biochemical, and cellular functions and pathways, running the gamut from transmembrane flux regulation of cations and anions, hormone-receptor bindings, cellular energy generation, muscle contraction, nerve impulse conduction, regulation of DNA and RNA structure and synthesis, regulation of carbohydrate, protein and lipid metabolism, regulation of cell growth and cell death pathways, and regulation of vascular tone and blood pressure [48,64-72].

Most importantly, the daily dietary intake of Mg has been steadily decreasing in the USA, UK, Europe and Russia since the turn of the last century from about 450 - 550 mg/day to about 135 - 235 mg/day. Normally, Mg exists in three forms: free or ionized; complexed to small anions (i.e., HCO_3^- , PO_4 , acetates, etc.); and protein-bound [73]. The free or ionized form is the physiologically-active Mg in the body. Up until our work, there were no reliable methods to measure all three fractions of Mg, particularly in the ER, OR, critical care units, and stroke units [73]. Thus, measurement of only total Mg in the blood is often very misleading. From the above, it is now our contention that people ingesting diets low in Mg, as many of those individuals (particularly the youth) who inject, imbibe, snort, main-line or ingest AM, METH and Ecstasy-like drugs, could be expected to demonstrate potential risk for strokes, brain damage, memory and cognitive losses, hallucinations, severe headaches, and heart attacks.

Conclusions and Future Thoughts

Although there seems to be an increased awareness of the overdoses and deaths from fentanyl in Western societies, little emphasis is, unfortunately, being devoted to warning the public about the very dangerous recreational use of AM, METH and Ecstasy-like designer drugs. Our results on animals and human subjects not only point to the serious risks for IS and hemorrhagic strokes, but suggest a potential therapeutic solution with Mg. Our findings also suggest that, if our hypothesis is correct, then human subjects who are brought to the ER with brain ischemia or strokes, and severe headaches, should be tested for low ionized Mg levels in blood and brain (using ³¹P-NMRS) and should receive intravenous injections of MgSO₄. At the very least, clinical trials should be undertaken using sophisticated techniques for measurement of free ionized Mg levels in cells, blood and tissues, and to employ fast -MRS to record localized blood flow changes in the brain of AM, METH and Ecstasy victims.

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Bibliography

1. Sides H. "Ghost Soldiers: The Epic Account of World Wars II's Greatest Rescue Mission". Knopf Doubleday Publishing Group, New York (2001).
2. Marshall SLA. "Night Drop: The American Invasion of Normandy". Bantam, New York (1962).
3. Brunton L., *et al.* "R Goodman and Gilman's The Pharmacological Basis of Therapeutics". 13th Edition. McGraw Hill Professional Publishers. New York (2017).
4. Brust JCM. "Stroke and substance abuse". In: Stroke: Pathophysiology, Diagnosis, and Management. Churchill Livingstone, New York (1995): 979-1000.
5. Brust JCM. "Stroke and substance abuse". In: Uncommon Causes of Stroke, Bogouslavsky J, Caplan L, eds. Cambridge University Press, New York (2002): 132-138.
6. Lappin JM., *et al.* "Stroke and methamphetamine use in young adults: a review". *Journal of Neurology, Neurosurgery, and Psychiatry* 88.12 (2017): 1079-1091.
7. Altura BM., *et al.* "Alcohol-induced spasms of cerebral blood vessels: relation to cerebrovascular accidents and sudden death". *Science* 220.4594 (1983): 331-333.
8. Altura BM and Altura BT. "Alcohol, stroke and the cerebral circulation". *Alcohol Health Research World* 14 (1990): 223-235.
9. Altura BM and Altura BT "Role of magnesium and calcium in alcohol-induced hypertension and strokes as probed by in-vivo television microscopy, optical spectroscopy, ³¹P-NMR spectroscopy, and a unique magnesium ion-selective electrode". *Alcoholism: Clinical and Experimental Research* 18.5 (1994): 1057-1068.
10. Altura BM and Altura BT. "Association of alcohol in brain injury, headaches and stroke with brain-tissue and serum levels of ionized magnesium". *Alcohol* 19.2 (1999): 119-130.
11. Altura BM., *et al.* "Increased risk of stroke using marijuana-cannabis products: Evidence for dangerous effects on brain circulation and the unrecognized roles of magnesium". *Drugs and Alcohol Addiction* 1.1 (2018): 1-6.
12. Bonhoff C and Lewrenz H. "Ueber Werkamine". Springer-Verlag, Berlin. (1954).
13. Cahill DW., *et al.* "Intracranial hemorrhage with amphetamine abuse". *Neurology* 31 (1981): 1058-1059.
14. Perez Jr JA., *et al.* "Methamphetamine-related stroke: Four cases". *Journal of Emergency Medicine* 17.3 (1999): 469-471.

15. Altura BM, *et al.* "Amphetamines, methamphetamine and Ecstasy result in vasospasm and rupture of microvessels and ischemic, as well as hemorrhagic, strokes in the cerebral and medullary microcirculations in the rat brain: Unrecognized roles of magnesium and ceramides" (2019).
16. Weinberg J and Altura BM. "Morphine pretreatment influences reactivity of isolated rat arterial smooth muscle". *Substance and Alcohol Actions Misuse* 1.1 (1980): 71-82.
17. Altura BT, *et al.* "Are there opiate receptors in the microcirculation?" In: *Vascular Neuroeffector Mechanisms*, Bevan JA, ed. Raven Press, New York (1980): 338-340.
18. Altura BT and Altura BM "Phencyclidine, lysergic acid diethylamide, and mescaline: cerebral artery spasms and hallucinogenic activity". *Science* 212.4498 (1981):1051-1052.
19. Altura BM and Altura BT. "Pharmacologic inhibition of cerebral vasospasm in ischemia, hallucinogen ingestion, and hypomagnesemia: Barbiturates, calcium antagonists, and magnesium". *American Journal of Emergency Medicine* 1.2 (1983): 180-190.
20. Altura BT, *et al.* "Phencyclidine (angel dust) and sigma-opiate benzomorphans cause cerebral arterial spasm". *Proceedings of the National Academy of Sciences of the United States of America* 80.3 (1983): 865-869.
21. Altura BT and Altura BM. "Cerebrovasospasms induced by phencyclidine are prevented by calcium antagonists and magnesium". *Experimental and Clinical Research* 2 (1983): 52-56.
22. Altura BT and Altura BM "Effects of barbiturates, phencyclidine, ketamine and analogs on cerebral circulation and cerebrovascular muscle". *Microcirculation Endothelium Lymphatics* 1.2 (1984): 169-184.
23. Altura BM and Altura BT. "Alcohol, the cerebral circulation and strokes". *Alcohol* 1.4 (1984): 325-331.
24. Altura BM. "Alcohol, stroke, hypertension and the heart: Overview". *Alcohol* 1.4 (1984):321-323.
25. Altura BT, *et al.* "Identification of benzomorphan-k-opiate receptors in cerebral arteries which subserve relaxation". *British Journal of Pharmacology* 82.2 (1984): 459-466.
26. Altura BM, Altura BT "Alcohol, the cerebral circulation and vascular diseases". In: *Progress in Alcohol Res*, Parvez H. NVU Press, Amsterdam 1 (1985): 311-326.
27. Altura BM. "Pharmacology of the pulmonary circulation: An overview". In: *The Pulmonary Circulation in Health and Disease*, Will JA, ed. Academic Press, New York (1987): 79-95.
28. Altura BM and Altura BT "Cardiovascular actions in alcoholism and after acute administration of alcohol: Heart and blood vessels". In: *Alcoholism: Biochemical and Genetic Aspects*, Goede HW, Agarwal DP, eds. Pergamon Press, Elmsford (1989): 167-227.
29. Huang Q-F, *et al.* "Mg²⁺ protects against PCP-induced cerebrovasospasms and vascular damage in rat brain". *Minerals and Trace Elements* 9.1 (1990): 44-46.
30. Huang Q-F, *et al.* "Cocaine-induced cerebral vascular damage can be ameliorated by Mg²⁺ in rat brain". *Neuroscience Letters* 109.1-2 (1990): 113-116.
31. Huang Q-F, *et al.* "Magnesium ions prevent phencyclidine-induced cerebrovasospasms and rupture of cerebral microvessels: direct in-vivo microcirculatory studies on the brain". *Neuroscience Letters* 113.1 (1990): 115-119.
32. Altura BM and Altura BT. "Alcohol, stroke, and the cerebral circulation". *Alcohol World Health and Research* 14 (1991): 322-332.
33. Altura BM and Gupta RK. "Cocaine induces intracellular free Mg deficits, ischemia and stroke as observed by in-vivo ³¹P-NMR of the brain". *Biochimica et Biophysica Acta* 1111.2 (1992): 271-274.
34. Altura BM, *et al.* "Alcohol intoxication results in rapid loss in free magnesium in brain and disturbances in brain bioenergetics: relation to cerebrovasospasm, alcohol-induced strokes, and barbiturate-induced deaths". *Magnesium and Trace Elements* 10.2-4 (1992): 122-135.
35. Zhang A, *et al.* "Alcohol-induced contraction of cerebral arteries in diverse mammals and its mechanisms of action". *European Journal of Pharmacology* 248.3 (1993): 229-236.

36. Altura BM, *et al.* "Cocaine induces rapid loss of intracellular free Mg in cerebral vascular smooth muscle cells". *European Journal of Pharmacology* 246.3 (1993): 299-301.
37. Altura BM, *et al.* "Ethanol promotes rapid depletion of intracellular free Mg in cerebral vascular smooth cells: Possible relation to alcohol-induced behavioral and stroke-like effects". *Alcohol* 10.6 (1993): 563-566.
38. Barbour RL, *et al.* "Optical spectroscopy and cerebral vascular effects of alcohol in intact brain: effects on tissue deoxyhemoglobin, blood content and reduced cytochrome oxidase". *Alcohol Clinical and Experimental Research* 17.6 (1993): 1319-1324.
39. He G-Q, *et al.* "Cocaine-induced cerebrovasospasm and its mechanism of action". *Journal of Pharmacology and Experimental Therapeutics* 268.3 (1994): 1532-1539.
40. Altura BM, *et al.* "Role of brain [Mg²⁺] I in alcohol-induced hemorrhagic stroke in a rat model: a 31P-NMR in-vivo study". *Alcohol* 12.2 (1995): 131-136.
41. Altura BM, *et al.* "Alcohols induce rapid depletion of intracellular free Mg in cerebral vascular muscle cells: relation to chain length and partition coefficient". *Alcohol* 12.3 (1995): 247-250.
42. Ludvig N, *et al.* "The suppressant effect of ethanol, delivered via intrahippocampal microdialysis, on the firing of local pyramidal cells in freely moving rats". *Alcohol* 12.5 (1995): 417-421.
43. Altura BM, *et al.* "Euphoria from drinking alcoholic beverages may be due to reversible constriction of cerebral blood vessels: potential roles of unrecognized ionized hypomagnesemia, and release of ceramides and platelet-activating factor". *Clinical Research and Trials* 2.6 (2016): 242-245.
44. Altura BM, *et al.* "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". *Cardiovascular Therapy: Open Access* 1.3 (2016): 112.
45. Altura BM, *et al.* "Stroke: A real danger from the therapeutic use of psychedelic drugs and the role of magnesium depletion". *EC Pharmacology and Toxicology special Issue* 01(2018): 18-23.
46. Altura BM, *et al.* "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". *Sci Fed Journal of Addiction and Therapy* 2.1 (2018): 1000009.
47. Kringelbach ML and Berridge KC "The joyful mind". In: *From Abuse to Recovery: understanding Addiction*. Macmillan, New York (2013): 199-207.
48. Altura BT and Altura BM. "The role of magnesium in etiology of strokes and cerebral vasospasm". *Magnesium* 1 (1982): 277-291.
49. Mauskop A and Altura BM. "Magnesium for migraine". rationale for use and treatment". *CNS Drugs* 9.3 (1998):185-190.
50. Mauskop A, *et al.* "Serum ionized magnesium levels in patients with tension-type headaches". In: *Tension-type Headache: Classification, Mechanisms and Treatment*. Olesen J, Schoenen J, eds. Raven Press, New York (1992): 137-140.
51. Mauskop A, *et al.* "Deficiency in serum ionized Mg but not total Mg in patients with migraine: Possible role of ICa²⁺/Mg²⁺ ratio". *Headache* 33.3 (1993): 135-138.
52. Mauskop A, *et al.* "Chronic daily headache-one disease or two? Diagnostic role of serum ionized magnesium". *Cephalgia* 14.1 (1994): 24-28.
53. Altura BT, *et al.* "Clinical studies with the NOVA ISE for Mg²⁺". *Scandinavian Journal of Clinical and Laboratory Investigation* 217 (1994): 53-67.
54. Mauskop A, *et al.* "Ionized Mg, total Mg and ICa²⁺/Mg²⁺ ratios in patients with episodic and chronic cluster headaches". *Headache Quarterly* 5 (1994): 156-158.
55. Mauskop A, *et al.* "Intravenous magnesium sulfate relieves migraine attacks in patients with low serum ionized magnesium levels: A pilot study". *Clinical Science* 89.6 (1995): 633-636.

56. Mauskop A, *et al.* "Intravenous magnesium relieves cluster headaches in patients with low serum ionized magnesium levels". *Headache* 35.10 (1995): 597-600.
57. Mauskop A, *et al.* "Intravenous magnesium sulfate relieves headaches of various types". *Headache* 36.3 (1996): 154-160.
58. Altura BM and Altura BT. "Role of magnesium in patho-physiological processes and the clinical utility of magnesium ion selective electrodes". *Scandinavian Journal of Clinical and Laboratory Investigation* 224 (1996): 211-234.
59. Mauskop A, *et al.* "Serum ionized magnesium as a biological marker in patients with headaches". *Headache Quarterly* 7.2 (1996): 142-144.
60. Chipperfield B and Chipperfield JR. "Relation of myocardial metal concentration to water hardness and death rates from ischaemic heart disease". *Lancet* 2.8145 (1979): 709-712.
61. Altura BM and Altura BT. "New perspectives on the role of magnesium in the pathophysiology of the cardiovascular system. I. Clinical aspects". *Magnesium* 4.5-6 (1985): 226-244.
62. Marier JR and Neri LC. "Quantifying the role of magnesium in the relationship between human mortality/morbidity and water hardness". *Magnesium* 4.2-3 (1985): 53-59.
63. Leary WP. "Content of magnesium in drinking water and deaths from ischemic heart disease in White South Africans". *Magnesium* 5.3-4 (1986): 150-153.
64. Altura BM and Altura BT. "Magnesium: Forgotten mineral in cardiovascular biology". In: *New Perspectives in Magnesium Research*. Springer, New York (2007): 239-260.
65. de Baaj JHE, *et al.* "Magnesium in man: Implications for health and disease". *Physiological Reviews* 95.1 (2015):1-46.
66. Altura BM and Altura BT. "Role of magnesium in contractility of blood vessels". *Magnesium Bulletin* 3 (1981): 102-114.
67. Altura BM and Altura BT. "Magnesium and vascular tone and reactivity". *Blood Vessels* 15.1-3 (1978): 5-6.
68. Turlapaty PDMV and Altura BM. "Magnesium deficiency produces spasms of coronary arteries; relationship to etiology of sudden death ischemic heart disease". *Science* 208.4440 (1980): 198-200.
69. Altura BM, *et al.* "Magnesium deficiency and hypertension: correlation between magnesium deficiency diets and microcirculatory changes in situ". *Science* 223.4642 (1984): 1315-1317.
70. Altura BM and Altura BT. "Magnesium and cardiovascular biology: an important link between cardiovascular risk factors and atherogenesis". *Cellular and molecular biology research* 41.5 (1995): 347-359.
71. Saris NE, *et al.* "Magnesium: an update on physiological, clinical and analytical aspects". *Clinica Chimica Acta* 294.1-2 (2000): 1-26.
72. Long S and Romani AM. "Role of magnesium in health and disease". *Austin Journal of Nutrition and Food Sciences* 2.10 (2014): 1051.
73. Altura BT and Altura BM. "A method for distinguishing ionized, complexed, and protein-bound Mg in normal and diseased subjects". *Scandinavian Journal of Clinical and Laboratory Investigation* 217 (1994): 83-87.

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