Drugs and Alcohol Addiction

COMMENTARY

Increased Risk of Stroke using Marijuana-Cannabis Products: Evidence for Dangerous Effects on Brain Circulation and the Unrecognized Roles of Magnesium

Burton M Altura[1-7], Asefa Gebrewold[1,5], Anthony Carella[1], Nilank C Shah[1,5], Bella T. Altura[1,3-7]

[1]Department of Physiology and Pharmacology
[2]Department of Medicine
[3]The Center for Cardiovascular and Muscle Studies
[4]The School of Graduate Studies in Molecular and Cellular Science, the State University of New York Downstate Medical Studies, Brooklyn, New York, Brooklyn, New York
[5]Bio-Defense Systems, Inc, Rockville Centre, New York
[6]Orient Biomedica, Estero, Florida
[7]Magnesium for Health Foundation, Patterson, California

Introduction

As of this year, eight states in The USA have approved "recreational use" of marijuana-cannabis whereas 19 states have approved the use of these drugs (and by-products) for medicinal purposes. Right-now, the two most-abused drugs in the USA are alcohol and marijuana. Both have been associated with an increased number of deaths worldwide each year. Marijuana has been used by indigenous tribes for many centuries for medicinal purposes. Although there is a great deal of both clinical and experimental evidence for involvement of alcohol as either a cause of strokes or as a contributing factor [1-4], the evidence for marijuana-cannabis as a causal factor in strokes has been controversial [5-10]. Very recently, using single photon emission computed tomography, Amen and his colleagues, studying approximately 1,000 current or former marijuana users, reported that the right part of the hippocampus, in the human brain, demonstrated decreases in blood flow [11]. Little known is that during the first hour of ingestion, cannabis increases the risk of myocardial infarction almost 5-fold [10]. In addition, ingestion of marijuana-cannabis products causes steep-rises in blood pressure (i.e., hypertension), tachycardia, and paroxysmal atrial fibrillation, among other cardiovascular untoward events [10]. 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 marijuana-cannabis as causal factors in, particularly, ischemic strokes (IS) and hemorrhagic strokes. We also present new evidence for, what we believe are, underlying biochemical and molecular pathways by which marijuana-cannabis probably produce IS.

It is a wide-perception that either ingestion or the smoking of marijuana is completely safe. Unfortunately, this perception appears to be particularly wide-spread among the youth (e.g., children below the age of 18). However, more than 30 years ago, it was first reported in young subjects that long-term smoking of marijuana caused stroke [6]. Over the intervening years, up to the present day, there have been a number of scattered reports, in the literature, which suggest that increasing use of marijuana can cause strokes [4, 6-10, 12-16]. Based on these reports, and others, the incidence seems to vary between 1.5- 25%, although these numbers appear very "iffy". A major problem in pin-pointing the active psychotomimetic aspects of marijuana is that there are at least 61 cannabinoids that have been identified [for recent reviews, see 17, 18]. However, one of these substances, namely delta9-tetrahydrocannabinol (delta 9-THC) appears to produce most of the psychotomimetic effects when smoked [17, 18]. It is clear that the degree(s) of the pharmacological effects of this molecule varies with the dose, route of administration, the setting, experience of the user, and vulnerability of the user for psychoactive drugs [17, 18].

For more than 30 years, smoking marijuana has been associated with hypotensive episodes and interference with autonomic reflexes [for reviews, se 17, 18]. Recent clinical studies are suggestive of profound cardiac effects [17, 18]. A number of physicians and investigators have long-suspected that long-term smoking-ingestion of marijuana-cannabis causes IS by virtue of their ability to induce cerebral vasoconstriction and vasospasm [7, 10, 13-15]. However, studies using measurement of cerebral vascular pulse-wave velocities seem

Correspondence to: BM Altura, Department of Physiology and Pharmacology, SUNY Downstate Medical Center, Brooklyn, New York, USA; Tel: 718-270-2194; Email: burton[DOT]altura[AT]downstate[DOT]edu

Received: Feb 12, 2018; **Accepted:** Feb 14, 2018; **Published:** Feb 16, 2018

to suggest a vasodilator rather than vasoconstrictor action, thus forming a factor leading to considerable controversy [17, 18]. As is shown below, we believe this controversy is a result of differential actions of marijuana-cannabis on brain regional circulation, microvascular vessel types, and local brain reflexes. These new experimental studies point out the potential dangers of long-term use of marijuana-cannabis preparations and potential mechanisms whereby these widely-abused drugs cause IS and hemorrhagic strokes. We believe our new studies confirm why marijuana-cannabis preparations should be strictly-controlled by Drug-Enforcement Agencies worldwide and why the public, particularly the youth, must be widely informed about the dangerous use of these drugs. The DEA classifies marijuana as a Schedule I drug, meaning it is highly dangerous with no known antidote(s) [17, 18]. Schedule I drugs include heroin and LSD.

Experimental Studies Demonstrate Marijuana-Cannabis Can Result in Regional Vasoconstriction-Vasospasm in Brain and Ischemic Stroke: Beneficial Effects of Magnesium

Using anesthetized rats, and exposure of the pial-brain microcirculation as well as vascular smooth muscle cells (VSMc) obtained from rats, dogs and monkeys, we have found that a variety of drugs of abuse (including all hallucinogens so far tested), including alcohol, LSD, heroin, PCP, psilocybin, cocaine, peyote, methamphetamine, 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[1, 19- 42]. In addition, using high-resolution, quantitative in-vivo television microscopy (at magnifications up to 6,400 x -normal) we have reported that these drugs of abuse can induce rupture of postcapillary venules with transudation of blood formed-elements, including red blood cells, into the surrounding perivascular tissues [1, 2, 24-26, 28-30, 32, 34-36, 38, 40, 42]. These reactions clearly are characteristics of a hemorrhagic stroke. Interestingly, pretreatment with either oral administration of Mg aspartate HCl or i.v. administration of this Mg salt prevented many of the stroke-like actions of these drugs of abuse [21, 24, 28-32, 39, 40, 42]. These conclusions were supported using ^{31}P-nuclear magnetic resonance spectroscopy (31P-NMR) and proton NMR spectroscopy on the intact brains of rats [29-31, 34, 35, 38, 39]. In addition, and most importantly, we found that prior to induction of stroke in the rat brains, we noted a precipitous rise in inorganic phosphorus content followed by reductions in both intracellular pH and ATP prior to hemorrhage and subsequent death [30,31,35, unpublished data]. In view of these extensive *in-vivo* and *in-vitro* findings, we decided to determine whether administration of marijuana-cannabis would yield similar reactions in the pial, medulla and cerebellar microvasculatures using a non-bleeding scrape-down method [43] for access to these intact microvasculatures.

So far, we have found that local administration and intra-arterial administration of both marijuana and purified 9-delta-cannabinol can produce dose-dependent constriction and spasm of the medullary and cerebellar microvasculatures, but often vasodilation of microvessels in the cerebral-pial microvasculature [45]. This vasoconstriction in the medullary microcirculation was often followed by blockage of medullary microvessels consisting of clumping of blood -formed elements in the postcapillary microvessels, and adherence of leukocytes and macrophages to the inner walls of the postcapillary venules in the medulla [45]. Such results, representative of inflammatory responses, could indicate the beginnings of hemorrhagic or ischemic strokes. However, these *in-vivo* studies have to be confirmed and extended before the latter could be taken as factual. Using new technology to implant electrodes in the hippocampal region of the freely moving rat brain, we found that ethanol suppressed the firing of numerous pyramidal neurons in a dose-dependent manner [37, 41]. Preliminary studies using other drugs of abuse indicate similar actions. We believe if such data are confirmed, in humans, this would suggest a reasonable rationale for disturbances of memory functions after ingesting a multitude of drugs of abuse, including marijuana and cannabis preparations. In addition, our studies could be used to suggest that these effects on the pyramidal neurons, in the hippocampus, could help to explain why marijuana-cannabis leads to long-lasting cognitive and behavioral deficits. Moreover, such effects on pyramidal brain cells would portend potential, irreversible damage to deep areas in the brain like the hippocampus. The stroke-like responses, in the medullary and cerebellar brain areas, were found by our group, to be dependent on the cellular entry and intracellular release of calcium ions [44], similar to that found for alcohol and hallucinogenic drugs [19, 21, 24-26, 30, 33, 35, 38]. Interestingly, marijuana-cannabis also resulted in some cellular Mg depletion in astrocytes and hippocampal brain slices [45].

Potential Role of Vasospasm and Hypomagnesemia in Marijuana-Cannabis -induced Euphoria 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 marijuana -smoking, alcohol, and other drugs/compounds (e.g., psychoactive drugs, designer drugs, stimulants, etc.) occurs via stimulation of hedonic hotspots within the brain's overall reward system [17, 18]. Interestingly, asphyxiation initially produces an intense feeling of euphoria, often leading people to intentionally induce asphyxiation and erotic sensations (i.e., brief episodes of hypoxia). Our findings of reversible/irreversible marijuana-cannabis -induced vasospasm of microvessels in the cerebellum and medulla, of living rat brains, would be enough to curtail blood 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, smoking or ingesting marijuana-cannabis will reversibly induce vasoconstriction/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 the marijuana-cannabis-induced reductions in intracellular free Mg, discussed above, would help to trigger the latter events.

Importance of Mg to Body Homeostasis, Cell Normalcy and Headaches

Low Mg content in drinking water 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 [46-55]. In this context, it is important to point out, here, that our group has found that strokes in humans, brain trauma in both animals and humans (with and without PCP, psilocybin, LSD, mescaline, peyote extracts, cocaine, methamphetamine, alcohol, or multi-drug use) all have shown deficits in blood ionized Mg levels [38, 42, 55-60]. Our findings on humans high on marijuana-cannabis (coming into the ER) exhibit similar characteristics. Such drug-induced blood, low free Mg levels result in calcium overload which causes death of neurons, glial cells, endothelial cells and regional brain vascular smooth muscle cells as observed by histological investigation of appropriate brain sections, at least in animals. Interestingly, one of the after -effects (i.e., hallmarks) of ingestion or smoking of marijuana-cannabis products are often intense migraine headaches [17, 18]. In this context, we have reported (on hundreds of migraine patients) a profound deficit in serum Mg^{2+} levels [61-64]; all migraine patients presenting with low serum ionized Mg had their headaches rapidly relieved with intravenous administration of magnesium sulfate [62-64].

Mg is a co-factor for more than 500 enzymes, and it is the second most abundant intracellular cation after potassium. It is critical in numerous physiological, cellular and biochemical functions and systems, running the gamut from transmembrane fluxes 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 and tissue growth processes, diverse cardiac functions, regulation of vascular tone and blood pressure, and programmed cell death processes (e.g., apoptosis, necroptosis, among others) [65- 73]. Most importantly, the dietary intake of Mg has been decreasing steadily in the USA and Europe since 1900 [60, 65]. Mg exists, in the body, in three forms, i.e., free or ionized, complexed to small anions, and protein-bound [74]. The free or ionized form is the physiologically-active and most important form in the body. Up until 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, critical-coronary care units, and stroke-units. We have noted that numerous patients admitted to our hospital ERs with suspected drug overdoses (and stroke-like symptoms) usually presented with significantly lowered ionized Mg levels, but not usually any deficits in total blood Mg levels. So, measurement of only total blood Mg levels usually is very misleading, as often no changes are noted, suggesting falsely, that Mg metabolism must be normal. From the above, it is now our contention that people ingesting diets low in Mg, as many of those individuals who smoke or ingest marijuana-cannabis preparations, could be expected to demonstrate potential risk for cerebral and coronary vasospasms along with advanced atherosclerosis in cerebral, medullary, cerebellar, and coronary arteries, thereby presenting with increased risk for stroke, brain damage, coronary arterial blockages, heart attacks, and sudden death.

Conclusions and Future Thoughts

Although there seems to be a renewed effort to open-up multiple sites (stores) in the USA and elsewhere for purchase of marijuana-cannabis products, without oversight of either physicians or healthcare personnel, or for use in treatment of patients with uncontrollable pain problems, to our knowledge, no warnings either written or verbal warn the potential user(s) of their very real dangers (reviewed above) to well-being and life-threatening stroke-and brain-damaging effects. Marijuana and cannabis products can result in numerous adverse brain circulatory actions in mammals when studied in living animals and on diverse isolated mammalian cerebral blood vessels, including sub-human primates. We believe, strongly, that in view of the findings reviewed above in humans and experimental animals, caution must be exercised by the uninformed public. At the very least, clinical trials should be undertaken on human volunteers using sophisticated physiological monitoring techniques, such as ^{31}P-NMR spectroscopy, near-infrared spectroscopy, magnetic resonance spectroscopy (MRS) as well as fast-MRS to record localized regional brain blood flows and brain metabolism to protect all potential users (recreational and patient users). Lastly, it would be propitious for all investigators and physician -scientists who plan to test marijuana-cannabis products that blood ionized Mg levels are carefully monitored.

Acknowledgement

We are indebted to several pharmaceutical companies who gave us (i.e., BMA and BTA) unrestricted grant support that helped to make our studies possible (i.e., SANDOZ Pharmaceuticals, the Upjohn Co., and Bayer Pharmaceuticals). Some of our original studies, discussed above, were supported, in part, by Research Grants from The N.I.M.H. and The N.I.H. Institute on Drug Abuse and The National Institute on Alcoholism and Alcohol Abuse. Many of the studies gestated while two of us (BMA and BTA) were at The Albert Einstein College of Medicine of Yeshiva University.

References

1. Altura BM, Altura BT (1983) Alcohol-induced spasms of cerebral blood vessels: relation to cerebrovascular accidents and sudden death. *Science* 220: 331-333. [View Article]

2. Altura BM, Altura BT (1984) Alcohol, the cerebral circulation and strokes. *Alcohol* 1: 325-331. [View Article]

3. Brust JM (1998) Stroke and substance abuse. In: Barnett HJM, et al. (Eds.), Stroke: Pathophysiology, Diagnosis, and Management, (3rd Edn,), Churchill Livingstone, UK, pp. 79-1000. [View Article]

4. Mc Carron MO, Thomas AM (1997) Cannabis and alcohol in stroke. *Postgrad Med J* 73: 448. [View Article]

5. Geller T, Loftis L, Brink DS (2004) cerebellar infarction in adolescent males associated with acute marijuana use. *Pediatrics* 113: e365-e370. [View Article]

6. Cooles P, Michaud R (1987) Stroke after heavy cannabis smoking. *Postgrad Med J* 63: 511. [View Article]

7. Zachariah SB (1991) Stroke following marijuana smoking. *Stroke* 22: 406-409. [View Article]

8. White D, Martin D, Geller T, et al (2000) Stroke associated with marijuana abuse: a case report. *Cerebrovasc Dis* 11: 284-285. [View Article]

9. Avaro LC, Iriodo I, Vilaverde FJ (2002) Sexual headache and stroke in a heavy cannabis smoker. *Headache* 42: 224-226. [View Article]

10. Mateo I, Pinedo A, Gomez Beldarrain M, Basterretxea JM, Garcia Monco JC (2005) Recurrent stroke associated with cannabis use. *J Neurosurg Psychiatry* 76:435-437. [View Article]

11. Amen DG, Darmal B, Raji CA, Bao W, Jorandby L, et al. (2017) Discriminative properties of hippocampal hypoperfusion in marijuana users compared to healthy controls: Implications for marijuana administration in Alzheimer's dementia. *J Alzheimer's Dis* 56: 261-273. [View Article]

12. Marnella MA (2001) Stroke after marijuana smoking in a teenager with factor V Leiden mutation. *South Med J* 94: 1217-1218. [View Article]

13. Brink D, Manepalli A, Geller T, Vogler C (2001) Cerebellar infarction associated with marijuana use in adolescent children. *Mol Pathol* 14: 5P. [View Article]

14. Brust JCM (1993) Marijuana. In: Butterworths Heinemann, et al. (Eds.). Neurological Aspects of Substance Abuse. [View Article]

15. Barnes D, Palace J, O'Brien MD (1992) Stroke following marijuana smoking. *Stroke* 23:1381. [View Article]

16. Kalla A, Krishnamoorthy P, Gopalakrishnan A, Figueredo VM (2017) Cannabis use predicts risk of heart failure and cerebrovascular accidents: results from the National Inpatient Sample. *J Am Coll Cardiol* 69: 1784. [View Article]

17. O'Brien CP (2018) Drug use disorders and addiction. In: Brunton LL, et al. (Eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics, (13th edn,), McGraw Hill Education, New York, USA, pp. 432-442. [View Article]

18. Nichols DE (2016) Psychedelics. *Pharmacol Rev* 68: 264-355. [View Article]

19. Altura BT, Altura BM (1981) Phencyclidine, lysergic acid diethylamide, and mescaline: cerebral artery spasms and hallucinogenic activity. *Science* 212: 1051-1053. [View Article]

20. Altura BM, Altura BT, Carella A, Chatterjee M, Halevy S, et al. (1982) Alcohol produces spasms of human umbilical blood vessels: relationship to fetal alcohol syndrome. *Eur J Pharmacol* 86: 311-312. [View Article]

21. Altura BT, Altura BM (1983) Cerebrovasospasm induced by phencyclidine are prevented by calcium antagonists and magnesium ions. *Magnesium Experimental Res* 2: 52-56. [View Article]

22. Altura BT, Quirion R, Pert CB, Altura BM (1983) Phencyclidine ("angel dust") analogs and sigma opiate benzomorphans cause cerebral arterial spasm. *Proc Nat Acad Sci USA* 80: 865-869. [View Article]

23. Altura BM, Altura BT, Carella A (1983) Ethanol produces coronary vasospasm: Evidence for a direct action of ethanol on vascular muscle. *Br J Pharmacol* 78: 260-262. [View Article]

24. Altura BM, Altura BT (1983) Pharmacologic inhibition of cerebral vasospasm in ischemia, hallucinogen ingestion, and hypomagnesemia: Barbiturates, calcium antagonists, and magnesium. *Am J Emerg Med* 1: 180-190. [View Article]

25. Altura BT, Altura BM (1984) Effects of barbiturates, phencyclidine, ketamine and analogs on cerebral circulation and cerebrovascular muscle. *Microcirc Endothelium Lymphatics* 1: 169-184. [View Article]

26. Altura BM, Altura BT (1985) Alcohol, cerebral circulation and vascular disease. In: Parvez H, et al, (Eds.). Progress in Alcohol Research, vol 1: Alcohol, Nutrition and the Nervous System, NVY Science Press, Amsterdam, The Netherlands, pp. 311-326. [View Article]

27. Altura BM, Altura BT (1989) Cardiovascular functions in alcoholism and after acute administration of alcohol: Heart and blood vessels. In: Goedde HW, et al. (Eds.). Alcoholism: Biochemical and Genetic Aspects, Pergamon Press, New York, USA, pp. 167-227. [View Article]

28. Huang QF, Gebrewold A, Altura BT, Altura BM (1990) Magnesium ions prevent phencyclidine-induced cerebrovasospasm and rupture of cerebral microvessels: Direct *in-vivo* microcirculatory studies on the brain. *Neurosci Lett* 113: 115-119. [View Article]

29. Altura BM, Altura BT (1991) Alcohol, stroke, and the cerebral circulation. *Alcohol* 14: 322-332. [View Article]

30. Altura BM, Altura BT (1994) Role of magnesium and calcium in alcohol -induced hypertension and strokes as probed by in vivo television microscopy, digital image microscopy, optical spectroscopy, 31P-NMR spectroscopy and a unique magnesium ion-selective electrode. *Alcoholism Clin Exp Res* 18: 1057-1065. [View Article]

31. Altura BM, Gebrewold A, Altura BT, Gupta RK (1995) Role of brain [Mg^{2+}]I in alcohol-induced hemorrhagic stroke in a rat model: a 31P-NMR *in vivo* study. *Alcohol* 12: 131-136. [View Article]

32. Huang QF, Gebrewold A, Altura BT, Altura BM (1990) Cocaine-induced cerebral vascular damage can be ameliorated by Mg^{2+} in rat brain. *Neurosci Lett* 109: 113-116. [View Article]

33. He GQ, Zhang A, Altura BT, Altura BM (1994) Cocaine-induced cerebrovasospasm and its mechanism of action. *J Pharmacol Exp Ther* 268: 1532-1539. [View Article]

34. Altura BM, Gupta RK (1992) Cocaine induces intracellular free Mg deficits, ischemia and stroke as observed by *in-vivo* 31P-NMR of the brain. *Biochim Biophys Acta* 1111: 271-274. [View Article]

35. Altura BM, Gebrewold A, Barbour RL, Altura BT, Gupta RK (1991) Alcohol intoxication results in rapid loss in free magnesium in brain and brain bioenergetics: Relation to cerebrovasospsm, alcohol-induced strokes and barbiturate anesthesia-induced deaths. *Magnes Trace Elem* 10: 122-135. [View Article]

36. Barbour RL, Gebrewold A, Altura BM (1993) Optical spectroscopy and cerebral vascular effects of alcohol in the intact brain: effects on tissue deoxyhemoglobin, blood content and reduced cytochrome oxidase. *Alcohol Clin Exp Res* 17: 1319-1324. [View Article]

37. Ludvig N, Altura BT, Fox SE, Altura BM (1995) The suppressant effect of ethanol, delivered via intrahippocampal microdialysis, on the firing of local pyramidal cells in freely behaving rats. *Alcohol* 12: 417-421. [View Article]

38. Altura BM, Altura BT (1996) Effects of alcohol on brain circulation. In: Begleiter H, et al. (Eds.). The Pharmacology of Alcohol and Alcohol Dependence, Oxford Univ Press, New York, USA, pp. 181-206. [View Article]

39. Altura BM, Gebrewold A, Altura BT, Gupta RK (1997) Magnesium protects against cocaine-induced hemorrhagic stroke in a rat model: A 31P-NMR *in-vivo* study. *Front Biosci* 2: 9-12. [View Article]

40. Ema M, Gebrewold A, Altura BT, Zhang A, Altura BM (1998) Alcohol-induced vascular damage of brain is ameliorated by administration of magnesium. *Alcohol* 15: 113-117. [View Article]

41. Ludvig N, Fox SE, Kube JL, Altura BM, Altura BT (1998). Application of the combined single-cell recording/intracerebral mictodialysis method to alcohol research in freely moving animals. *Alcohol Clin Exp Res* 22: 41-50. [View Article]

42. Altura BM, Altura BT (1999) Association of alcohol in brain injury, headaches and stroke with brain-tissue and serum levels of ionized magnesium. *Alcohol* 19(2): 119-130. [View Article]

43. Lassoff S, Gebrewold A, Altura BM (1982) A new method of craniotomy in the rat: *In-vivo* investigation of the pial microcirculation. *Microcirculation* 2: 345-353. [View Article]

44. Gebrewold A, Altura BT, Altura BM (2018) Marijuana and 9-delta tetrahydrocannabinol produce direct vasodilator and vasoconstrictor-spasm-like effects on the pial, cerebellar, and medullary microvasculatures of the living rat brain. Submitted. [View Article]

45. Altura BM, Zhang A, Li W, Babu A, Carella A, et al. (2018) Marijuana and 9-delta-teratahydrocannabinol alter Mg^{2+} levels in astrocytes and hippocampal neurons. Submitted. [View Article]

46. Chipperfield B, Chipperfield JR (1979) Relation of myocardial metal concentrations to water hardness, and death from ischaemic heart disease. *Lancet* 2: 709-712. [View Article]

47. Turlapaty PDMV, Altura BM (1980) Magnesium deficiency produces spasms of coronary arteries: relationship to etiology of sudden death ischemic heart disease. *Science* 208: 198-200. [View Article]

48. Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T (1984) Magnesium deficiency and hypertension: correlation between magnesium deficient diets and microcirculatory changes in situ. *Science* 223: 1315-1317. [View Article]

49. Marier JR, Neri LC (1985) Quantifying the role of magnesium in the interrelationship between human mortality/morbidity and water hardness. *Magnesium* 4: 53-59. [View Article]

50. Leary WP (1986) Content of magnesium in drinking water and deaths from ischemic heart disease in white South Africans. *Magnesium* 5: 150-153. [View Article]

51. Altura BT, Brust M, Bloom S, Barbour RL, Stempak JG, et al. (1990) Magnesium dietary intake modulates blood lipid levels and atherogenesis. *Pro Nat Acad Sci USA* 87: 1840-1844. [View Article]

52. Altura BM, Altura BT (1996) Role of magnesium in pathophysiological processes and the clinical utility of magnesium ion-selective electrodes. *Scand J Clin Lab Invest* 224: 211-234. [View Article]

53. Marx A, Neutra RR (1997) Magnesium in drinking water and deaths from ischemic heart disease. *Epidemiol Rev* 19: 258-272. [View Article]

54. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A (2000) Manesium. An update on physiological, clinical and analytical aspects. *Clin Chim Acta* 294: 1-26. [View Article]

55. Altura BM, Lewenstam A (1994) Unique Magnesium-Sensitive Ion Selective Electrodes. *Scand J Clin Lab Invest* 54(Suppl 217): 1-100. [View Article]

56. Memon ZI, Altura BT, Benjamin JL, Cracco RQ, Altura BM (1995) Predictive value of serum ionized but not total magnesium levels in head injuries. *Scand J Clin Lab Invest* 55: 671-677. [View Article]

57. Altura BM, Memon ZI, Altura BT, Cracco RQ (1995) Alcohol-associated acute head trauma in human subjects is associated with early deficits in serum ionized Mg and Ca. *Alcohol* 12: 433-436. [View Article]

58. Altura BT, Altura BM (1982) The role of magnesium in etiology of strokes and cerebrovasospasm. *Magnesium Exp Clin Res* 1: 277-291. [View Article]

59. Altura BT, Memon ZI, Zhang A, Cheng TPO, Siverman R, et al. (1997) Low levels of serum ionized magnesium are found in patients early after stroke which results in rapid elevation in cytosolic free calcium and spasm in cerebral vascular smooth muscle cells. *Neurosci Lett* 230: 37-40. [View Article]

60. Altura BM, Altura BT (2007) Magnesium: Forgotten mineral in cardiovascular biology and atherogenesis. In: Morii H, et al. (Eds.). New Persp Mag Res, Springer, UK, pp. 239-260. [View Article]

61. Mauskop A, Altura BT, Cracco RQ, Altura BM (1993) Deficiency in serum ionized Mg but not total Mg in patients with migraines: Possible role of Ca^{2+}/IMg^{2+} ratio. *Headache* 33: 135-138. [View Article]

62. Mauskop A, Altura BT, Cracco RQ, Altura BM (1995) Intravenous magnesium sulfate relieves migraine attacks in patients with low serum ionized magnesium levels: a pilot study. *Clin Sci* 89: 633-636. [View Article]

63. Mauskop A, Altura BT, Cracco RQ, Altura BM (1996) Intravenous magnesium sulfate rapidly alleviates headaches of various types. *Headache* 36: 154-160. [View Article]

64. Mauskop A, Altura BT, Cracco RQ, Altura BM (1996) Serum ionized magnesium as a biological marker in patients with headaches. *Headache Quarterly* 7: 142-144. [View Article]

65. Altura BM, Altura BT (1995) Magnesium and cardiovascular biology: An important link between cardiovascular risk factors and atherogenesis. *Cell Mol Biol Res* 41: 347-360. [View Article]

66. Altura BM (1994) Introduction: importance of magnesium in physiology and medicine and the need for ion selective electrodes. *Scand J Clin Lab Invest* 54(Suppl 217): 5-10. [View Article]

67. Altura BM, Altura BT (1995) Magnesium in cardiovascular biology. *Sci Am Sci Med* 2: 28-37. [View Article]

68. Altura BM, Altura BT (2009) Atherosclerosis and magnesium. In: Calcium and Magnesium in Drinking Water. *WHO Geneva*: 75-81. [View Article]

69. Altura BM, Shah NC, Li Z, Jiang XC, Perez Albela JL, et al. (2009) Short term magnesium deficiency results in decreased levels of serum sphingomyelin, lipid peroxidation, and apoptosis in cardiovascular tissues. *Am J Physiol Heart Circ Physiol* 292: H86-H92. [View Article]

70. Emila S, Swaminatha S (2013) Role of magnesium in health and disease. *J Exp Sci* 4: 32-43. [View Article]

71. Long S, Romani AM (2014) Role of cellular magnesium in human disease. *Austin J Nutr Food* 2. [View Article]

72. de Baaij JHE, Hoenderop JG, Bindels RJ (2015) Magnesium in man. Implications for health and disease. *Physiol Rev* 95: 1-46. [View Article]

73. Altura BM, Shah N, Shah GJ, Altura BT (2017) Regulated RIPK3 necroptosis is produced in cardiovascular tissues and cells in dietary magnesium deficiency: Roles of cytokines and their potential importance in inflammation and atherogenesis. J Med Surg Pathol 2: e104. [View Article]

74. Altura BT, Altura BM (1994) A method for distinguishing ionized, complexed and protein-bound Mg in normal and diseased human subjects. Scand J Clin Lab Invest 54(Suppl 217): 83-88. [View Article]

Citation: Altura BM, Gebrewold A, Carella A, Shah NC, Altura BT (2018) Increased Risk of Stroke using Marijuana-Cannabis Products: Evidence for Dangerous Effects on Brain Circulation and the Unrecognized Roles of Magnesium. Drugs Alcohol Addict 1: 001-006.