COMMENTARY

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

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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

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 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].
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 patients). 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 Drug Abuse. Many of the studies gestated while two of us (BMA and BTA) were at The Albert Einstein College of Medicine of Yeshiva University.

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