

# Stroke: A Real Danger of the Therapeutic Use of Psychedelic Drugs and the Role of Magnesium Depletion

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For hundreds, if not thousands of years, plant-based psychedelic drugs, such as psilocybin and peyote, have been utilized for medicinal use [1-10]. In 1950, a report was published that lysergic acid diethylamide (LSD), and other psychedelic drugs could prove useful in the treatment of patients with psychological and psychiatric problems [1]. Many of these drugs have been recommended for mood disorders and drug dependence. LSD, initially, in the 1960's seem to demonstrate therapeutic effectiveness in some forms of mood disorders and drug-dependence [3,4]. Tens of thousands of human subjects have been subjected to "psychedelic therapy" for at least two decades [3-5,7]. Scientists in the U.S.A., Germany and Switzerland started a revival in the 1990's [5,7,8,11-16]. It appears, there has been an ever-increasing revival of using psychedelic drugs, such as LSD and ketamine and derivatives as well as psilocybin, in depressed subjects since the 1990's [17-26]. At least three clinical trials using psilocybin have been undertaken [16-19]. Most of these earlier trials had employed very small sample sizes. A meta-analysis of 19 psychedelic studies suggests that upwards of 75% of patients treated with psychedelics demonstrated positive improvement for mood disorders [19]. Several recent clinical trials suggest that several of the psychedelic drugs showed marked improvement in obsessive compulsive disorder symptoms, alcohol dependence, anxiety and depression [17-23,25,26]. Although these results, collectively, are enticing, very few, if any of these studies and trials, tell the reader/practitioner about deaths or dangerous side effects.

The main characteristic of these psychedelic drugs, including new designer psychedelics, are their "hallucinogenic properties" [1-9]. This characteristic has led to the illicit production of numerous, very potent psychedelics available on "the streets" at cheaper and cheaper prices". This has led to numerous deaths, particularly among the youngest generation. However, most of these patient deaths have not undergone autopsies. Almost 40 years ago, two of us reported that LSD, psilocybin, mescaline, peyote, "PCP", cocaine, alcohol, and methamphetamine administration to living rat brains, or in isolated cerebral arteries from dogs and primates, caused dose-dependent vasoconstriction and vasospasm, leading to rupture of intact cerebral microvessels under very high magnification, as observed in situ by quantitative TV image-intensification microscopy in our laboratories [27-33]. Interestingly, these stroke-like effects were found to take place in concentrations found in the bloods of human subjects administered several different mind-altering concentrations of the psychedelic drugs and numerous "designer drugs". Many of these reactions are accompanied by elevation in arterial blood pressure

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sometimes to dangerous levels in human subjects. After our original experimental findings were reported, other clinical investigators reported that several of the psychedelics appeared to cause strokes in human subjects [34]. Further investigation by our group, together with colleagues from The N.I.M.H., found that numerous synthetic analogs of ketamine, LSD and analogs, PCP, alcohol, cocaine, methamphetamine and heroin caused concentration-dependent vasospasm of cerebral arterioles and venules (25 - 100  $\mu\text{m}$  o.d. in size), followed by rupture of postcapillary venules *in vivo*, in the living rat brain microcirculation, using high-powered quantitative TV-image intensification (with magnifications up to 3,200x –normal) as well as on isolated canine and monkey cerebral arteries [27-33]. Careful TV video microscopy of the *in-situ* rat brains revealed that these hallucinogenic drugs resulted in adhesion of macrophages, monocytes, leukocytes and platelets on the postcapillary endothelial walls, often eventuating in increased vascular permeability of these blood-formed elements into the perivascular tissue spaces. The latter clearly is a result of inflammatory reactions in response to the drugs. This work, taken together with other studies, led us to postulate the existence of a new receptor, which we termed “a sigma-opiate benzomorphan receptor” [29].

These psychedelic-induced vasospasms and stroke-like effects were found, by our group, to be dependent on the entry and intracellular release of calcium ions [27,28,30,31]. Interestingly, we found that these drugs also resulted in cellular depletion of magnesium ions ( $\text{Mg}^{2+}$ ) [31,32,35]. Having the latter information, we decided to test the hypothesis that administration of  $\text{Mg}^{2+}$  might prevent/attenuate the stroke-like effects of the psychedelic drugs, including PCP, mescaline, psilocybin, ketamine and their analogs. Using the *in-vivo* rat brain microcirculation as a model, we have, indeed, found that  $\text{Mg}^{2+}$  administration, depending upon concentration, either attenuated the vasoconstrictor and stroke-like effects of these hallucinogenic drugs or inhibited, completely, their dangerous effects on the brain microcirculation [36]. Moreover, the inflammatory-like effects of these mood-altering drugs, in rodent brains, on the microcirculations of the cerebral cortex and medulla, were observed to be markedly attenuated [36].

Additional *in situ* studies on the cerebral microcirculation demonstrated that dietary deficiency of  $\text{Mg}^{2+}$  showed that very low doses (less than toxic levels) of LSD, psilocybin, peyote extracts, and PCP, surprisingly, produced stroke-like effects, resulting in vasospasm of precapillary microvessels and rupture of postcapillary venules, as well as sticking of white cells, macrophages and platelets to the inner endothelial walls of the latter microvessels, followed by transudation of fluid and formed elements into the surrounding parenchymal tissues [36].

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 artery vasospasm, hypertension and strokes [37-42]. In this context, it is of considerable interest to note, here, that we have found that strokes in humans, brain trauma in both humans and animals (with and without PCP, psilocybin, LSD, mescaline, peyote extracts, cocaine, methamphetamine, alcohol, or multi-drug use) all have shown deficits in brain tissue and blood ionized Mg levels [31,32,35-48]. These drug-induced brain-tissue free Mg levels result in calcium overload which causes death of neurons, astrocytes, glial cells, endothelial cells and cerebral vascular smooth muscle cells, as observed by histological tissue investigation of brain sections.

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 binding, 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 cell death processes (e.g. apoptosis, necroptosis, among others) [49-54]. Most importantly, the dietary intake of Mg has been decreasing steadily in the U.S.A. and Europe since 1900 [49-52,55]. It exists in three forms in the body; i.e. free or ionized, complexed to small anions, and protein-bound [56]. The free or ionized form is the physiologically-active and most important form in the body [49,51,56]. Up until our extensive studies, there were no reliable meth-

ods to rapidly measure the ionized Mg fraction in blood and other body fluids, particularly in the OR, critical-coronary care units, and stroke-care 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 or tissue Mg levels [42,45,48]. So, measurement of only total Mg levels usually is very misleading, as often no changes are noted suggesting, falsely, that Mg metabolism must be normal or near-normal.

## Conclusions and Future Thoughts

Although there seems to be a renewed effort to utilize mood-altering drugs and psychedelic drugs for treatment of patients with various psychological disturbances and disorders (reviewed above), none of these published studies or clinical trials has mentioned the potential stroke-like effects of these drugs. The psychedelic drugs, in these clinical trials, all result in numerous adverse brain circulatory actions in numerous mammals when studied in living animals and on diverse isolated cerebral blood vessels from these mammals, including sub-human primates. We believe, strongly, that in view of the findings reviewed, herein, caution must be exercised on patients entered into clinical trials employing psychedelic or mood-altering drugs. At the very least, effects on brain circulation and metabolism using sophisticated physiological monitoring techniques, such as <sup>31</sup>P nuclear magnetic resonance spectroscopy (<sup>31</sup>P-NMR), near-infrared spectroscopy, magnetic resonance imaging spectroscopy (MRI) as well as fast-MRI spectroscopy to record localized cerebral blood flows and cell metabolism in the brain, must be monitored to protect all patients from potential stroke-like effects of the psychedelic drugs and their analogs. Lastly, in view of our findings, it would be propitious for all investigators and psychiatrists who plan to test psychedelic drugs that blood ionized Mg levels are carefully monitored, and if found to be low, the mood-altering drugs should only be administered with extreme caution.

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