Spice, pot, and stroke

John C.M. Brust, MD

Correspondence to
Dr. Brust:
Jcb2@Columbia.edu

Neurology® 2013;81:2064–2065

The endocannabinoid system includes 2 types of G-protein coupled receptors: CB1 (mostly in the brain) and CB2 (in peripheral lymphoid tissue). The major cannabinoid ligands are arachidonylethanolamine ("anandamide," the Sanskrit word for bliss) and 2-arachidonylglycerol ("2AG"). It is by binding to CB1 receptors that δ-9-tetrahydrocannabinol (THC), the principal psychoactive ingredient in marijuana ("pot"), produces its intended subjective effects.

After the discovery of the endocannabinoid system 20 years ago, dozens of synthetic agonist and antagonist ligands were developed for pharmacologic research. It was not long before synthetic cannabinoids emerged as recreational drugs, legally available at head shops and gas stations and through the Internet. Collectively termed "spice" and "K2," preparations consist of one or more synthetic cannabinoid compounds sprayed onto a mixture of herbs and aromatic extracts, some of which might themselves have psychoactive properties. Alternatively, synthetic cannabinoids may be sold as single-ingredient powders.[1,2] Some spice products are contaminated with the β_2-adrenergic clenbuterol, perhaps accounting for sympathomimetic effects.[3]

When the increasing popularity of spice became recognized, the more widely abused synthetic cannabinoids were designated schedule I by the US Food and Drug Administration (FDA). Purveyors responded by creating pharmacologic analogs that would escape the FDA's jurisdiction until they could be chemically characterized. Products containing the original synthetic compounds (e.g., JWH-018, named after John W. Huffman, who developed it) are now illegal but still available, and hundreds of easily synthesized and quasi-legal derivatives have appeared on the market.[4] Carrying brand names such as "Bonzai," "Krypton," "Chillout Mint," and "Aroma," spice products are often labeled as "herbal blends" or "incense." In the United States, spice is now the second most used illicit drug (after marijuana) among high school seniors.[5]

Contributing to the popularity of spice is that synthetic cannabinoids are not identified in standard toxicology screens. Moreover, whereas THC is a partial agonist at CB1 receptors, many synthetic cannabinoids are full agonists with several times the potency or efficacy of THC. Reported adverse effects include agitation, hallucinations, psychosis, suicide, generalized convulsions, cardiac arrhythmias, myocardial infarction, and, upon abstinence, profuse sweating, nightmares, tremor, headache, and craving.[1,4,6]

In this issue of *Neurology*®, Freeman et al.[7] describe ischemic stroke in 2 healthy young siblings whose symptoms appeared within "a few minutes" or "a few hours" of smoking spice. Both were also marijuana users, and the authors acknowledge a possible causal role for unidentified toxins in the preparation, for marijuana itself, or for synergistic effects of marijuana and the synthetic cannabinoid.

Fifty-nine cases of marijuana-related stroke have been reported in the literature, and a population-based study of hospitalized patients found an adjusted odds ratio of 1.76 for marijuana exposure associated with ischemic stroke.[8,9] Proposed mechanisms include cardiac arrhythmia with embolism and, in several patients who underwent serial vascular imaging, reversible cerebral vasoconstriction syndrome (RCVS). (Conversely, of 67 patients with RCVS but without a clinical stroke, 20 were marijuana users.[10]) The strokes described by Freeman et al. appear to have been cardioembolic rather than the result of RCVS.

A reason for skepticism regarding anecdotal reports of marijuana-related stroke is how few there have been, given that marijuana is the most widely used illicit drug. The fact that the patients of Freeman et al. were siblings raises the intriguing possibility of genetic predisposition. In any event, if marijuana can cause ischemic stroke, and if anything pot can do spice can do better, neurologists will likely encounter increasing numbers of spice-associated strokes in the years ahead.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

The author reports no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

See page 2090

From the New York Neurological Institute and Columbia University College of Physicians & Surgeons, NY.

REFERENCES

1. Gunderson EW, Haughey HM, Ait-Daoud N, et al. "Spice" and "K2" herbal highs: a case series and systematic review of the clinical effects and biopsychosocial implications of synthetic cannabinoid use in humans. Am J Addict 2012;21:320–326.
2. Rosenbaum CD, Carreiro SP, Babu KM. Here today, gone tomorrow … and back again? A review of herbal marijuana alternatives (K2, spice), synthetic cathinones (bath salts), kratom, *Salvia divinorum*, methoxetamine, and piperazines. J Med Toxicol 2012;8:15–32.
3. Simmons JR, Skinner CG, Williams J, et al. Intoxication from smoking "spice." Ann Emerg Med 2011;57:187–188.
4. Papanti D, Schifano F, Botteon G, et al. "Spiceophrenia": a systematic overview of "spice"-related psychopathological issues and a case report. Hum Psychopharmacol 2013;28:379–389.
5. Johnson LD, O'Malley PM, Bachman JG, Schelenberg JE. Monitoring the Future: National Results on Adolescent Drug Use—Overview of Key Findings. Ann Arbor: The University of Michigan Institute for Social Research; 2011.
6. Seely KA, Lapoint J, Moran JH, Fattore L. Spice drugs are more than harmless herbal blends: a review of the pharmacology and toxicology of synthetic cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry 2012;39:234–243.
7. Freeman MJ, Rose DZ, Myers MA, Gooch CL, Bozeman AC, Burgin WS. Ischemic stroke after use of the synthetic marijuana "spice." Neurology 2013;81:2090–2093.
8. Wolff V, Armspach JP, Lauer V, et al. Cannabis-related stroke: myth or reality? Stroke 2013;44:558–563.
9. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. Arch Gen Psychiatry 2007;64:495–502.
10. Ducros A, Boukobza M, Porcher R, et al. The clinical and radiological spectrum of reversible cerebral vasoconstriction syndrome: a prospective series of 67 patients. Brain 2007;130(pt 12):3091–3101.