Cannabis sativa has been used in two main preparations—marijuana and hashish—for psychoactive properties for thousands of years. In 11th century Persia, Hassan Sabbah, head of the Ismailic sect of Shiite Islam, exploited hashish to enlist young men into his clandestine army of assassins. He described the euphoria of hashish as a semblance of paradise, a state to which they were destined upon successful completion of their missions. Notorious for consumption of hashish prior to their assignments, in Arabic they were called the Hash’shashin—the origin of the term “assassin.”

A 2008 survey found that 102 million Americans have used marijuana (cannabis) in their lifetimes; over 15 million use it regularly. In 1937, the US Marijuana Tax Act declared the use of marijuana illegal for any recreational or medicinal use. There is a well-defined dichotomy between those who support the legalization of cannabis in the US and those who are against it. The proponents’ claims range from the highly-publicized medical benefits of cannabis to assertions that it is “safer than tobacco.” Although therapeutic benefits of cannabis have not been persuasively established, there is evidence suggesting harmful effects associated with this drug. In this article, we will focus on the association of cannabis use and ischemic stroke (IS).

**Pharmacology and Pathogenesis of Vascular Disease**

The primary psychoactive ingredient of cannabis is delta(9)-tetrahydro-cannabinol (THC). Upon entering the systemic circulation, THC interacts with two receptors, the CB1 and the CB2. Central nervous system (CNS) responses are believed to be mediated by the G-protein-coupled CB1 subtype. CB1 receptors are particularly abundant in the frontal cortex, hippocampus, basal ganglia, and cerebellum. Activation of CB1 receptor inhibits the release of amino acid and monoamine neurotransmitters, leading to retrograde signal from postsynaptic to presynaptic neurons in the brain. This leads to the “high” associated with cannabis. CNS effects of cannabis include disruption of psychomotor behavior, short-term memory impairment, stimulation of appetite, anti-nociceptive, and anti-emetic effects. The plasma half-life of THC is approximately 56 hours in occasional users and 28 hours in chronic users.

CB1 and CB2 receptors are also widely distributed in the cardiovascular system. Activation of these receptors modulates the cellular activity of the vessel wall, which may contribute to the pathogenesis of atherosclerosis. CB1 expression has been identified in macrophages of advanced atheromas. Atherosclerotic coronary artery sections from patients with unstable angina have shown significantly higher expression of CB1 receptors in comparison to those with stable angina. THC has also been shown to activate platelets via CB1 and CB2 receptors, leading to increased GPIIb-IIIa expression and activation of factor VII, a potent thrombogenic protein.

A form of arteritis linked to marijuana use seems to differ from thromboangiitis obliterans (Buerger’s disease) associated with smoke inhalation. Consumption of marijuana has been identified as a trigger for acute myocardial infarction (MI). Risk of onset is increased 4.8 times over baseline in the 60 minutes after drug use, confirming the temporal relationship between cannabis and vascular events. Cannabis causes tachycardia with increased cardiac output and cardiac workload, creating an imbalance in myocardial supply and demand, subsequently leading to acute MI. Evidence suggesting a relationship between cannabis and vascular disease is abundant; summarizing all existing data is beyond the scope of this article.

**Association with Stroke**

A plethora of case reports and series describe the association of cannabis with IS. In a study of 218 New Zealanders with IS or transient ischemic attack (TIA), 25 (15.6 percent) had urine drug screens (UDS) positive for cannabis compared to 8.1 percent of control participants. In a logistic regression analysis adjusted for age, sex, and ethnicity, cannabis use was associated with an increased risk of IS or TIA. However, after adjusting for tobacco use, an association independent of tobacco could not be established. A recent review of literature by Wolff, et al. revealed 59 case reports of cannabis-related stroke; the majority being IS (83 percent). Mean age in this group was 33 years, and the ratio of men to women was 4.9 to 1. IS was more frequent in chronic than occasional users. Findings suggested a temporal association between cannabis consumption and IS, noting several reports that stroke occurred while the drug was actually being smoked or up to 30 minutes after the last joint had been smoked. In a case study of 17 IS patients who were exposed to marijuana, the causal relationship was justified by the absence of other vascular risk factors, a temporal
link between symptom onset and cannabis exposure, and the recurrence of symptoms with re-exposure. Another literature review by Desbois et al. noted 71 cases of cannabis users with IS. All patients were “heavy” marijuana smokers and in 76.5 percent, acute symptoms occurred during or within 30 minutes of consuming the drug.

The mechanism by which cannabis may cause IS is not completely understood, but there are theories. Aside from the development of atherosclerosis, THC may trigger reversible cerebral vasoconstriction syndrome (RCVS). Animal studies have shown THC has peripheral vasoconstrictor properties. Wolff, et al. reported the presence of multifocal intracranial stenosis in 21 percent of marijuana users who presented with IS. This form of cerebral angiopathy appeared to be reversible in three to six months following cessation of marijuana use. Desbois and colleagues reported multifocal stenosis in 50 percent of patients, solitary focal stenosis or occlusion in 22.6 percent, and RCVS in 43 percent. A retrospective review of patients with RCVS reported an incidence of 32 percent for cannabis-associated MI. Disruption of myocardial supply and demand equilibrium leading to ischemia was described earlier. There are, in all likelihood, multiple mechanisms for IS that are triggered or potentiated by THC. The reason why IS or other vascular events occur in some chronic users and not others may point to a predisposition, perhaps genetic, but still undetermined. At present, the only consistent feature of patients with cannabis-associated IS is male gender.

CONCLUSION

Evidence supporting the link between cannabis and IS is growing; a causal relationship is yet to be enacted. In addition to the chronicologic connection between consumption and onset of symptoms, perhaps the next most compelling evidence is relapses of IS with cannabis re-exposure. There are also peculiar vascular disease characteristics that can only be explained by cannabis use. For example, cannabinoid-associated limb arteritis occurs primarily in young men who excessively smoke marijuana. Compared with cohorts of thromboangiitis obliterans patients, those with cannabis-associated limb arteritis have more frequent unilateral involvement of the lower limbs at clinical presentation. The lack of epidemiological data is in part due to less than frequent UDS testing on IS patients. Even if UDS is positive, cannabis is often dismissed as a potential risk factor for IS. Also, concomitant abuse of other substances (cocaine, alcohol, opiates) can serve as a confounder, and the contribution of these drugs to the pathogenesis of IS cannot be underemined; even in chronic marijuana abusers. More work is needed to prove the cannabis connection. The incidence of IS vis-à-vis marijuana abuse is rare, and although this is good news, it creates a challenge for a large-scale, population-based study.

If a link is indisputably established, modulation of CB1 and CB2 receptors could become a therapeutic target in patients with vascular disease, including IS.

The only discernible utility of cannabis in medicine is in palliative care, not much else. There is no evidence that it has a scintilla of therapeutic benefit in any specific disease condition. Interestingly, the advocates of “medical marijuana” insist that the substance be smoked in order to receive maximal medicinal benefit. This exposes the individual to toxins associated with smoke inhalation. The American Society of Addiction Medicine maintains that there is no entity known as “medical marijuana.” Moreover, the Society warns against the many serious, well documented, negative health effects of this drug. So long as this societal statement and the Marijuana Tax Act exist, the incidence of IS associated with marijuana should remain low, even if the connection between the drug and the disease is loose.

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1. Substance Abuse and Mental Health Services Administration. 2008 National Survey on Drug Use and Health National Findings. Available at: http://www.oas.samhsa.gov/NSDUH/2k8NSDUH/NSDUH-tab06.htm