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Guest Articles

Impact of marijuana on human brain

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What is marijuana?

Marijuana, which is commonly called "pot, weed or Mary Jane" is a flowering plant in the *Cannabaceae* family. *Cannabaceae* family includes about 170 different species distributed among 11 genera, such as, Cannabis, Humulum, Celtis, Aphananthe, Chaetachme, Gironniera, Lozanella, Parasponia, Pteroceltis, Moraceae and Trema.[1] The genus Cannabis is famous for its two species *Cannabis sativa* and *Cannabis indica*. *Cannabis sativa* is commonly known as hemp, and it is also valued for its fibers, seeds and oil. *Cannabis indica* plants usually grows shorter and denser with wider leaves and higher THC (tetrahydrocannabinol) levels than the sativa plants. It is said that sativa plants are often associate with more energizing and stimulating effect on brain while indica species gives a sedative feeling. However, the effect of these plants does not completely depend on its species, but on the chemical composition of the plant as well. Apart from these two species, sativa and indica plants are also crossbred to create hybrid species, *Cannabis ruderalis*. This species exhibits a mixture of properties of its parent plants. They are also known as auto flowering plants as they can flower under any type of light, unlike photoperiodic sativa and indica species.[2] Figure 1 shows the physical differences between the species *Cannabis sativ*a, *Cannabis indica* and *Cannabis ruderalis*.

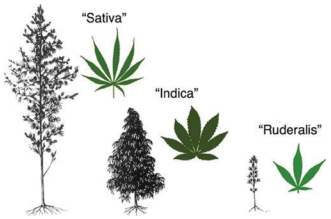

Figure 1: *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*.[3]

How is Marijuana used?

The delivery method of marijuana is important to optimize the mental and physical effects for medical marijuana users and for people using it recreationally, whether legally or not. Marijuana can be used in many ways; smoking, oral and topical are the three basic delivery methods that are been used. Marijuana smokers usually use hand rolled cigarettes called joints or water pipes which are called bongs. Some users also use marijuana blunts to smoke. These are made by replacing the tobacco in cigars by marijuana, often combining it with cocaine for more stimulation.[1] Oral delivery involves mixing marijuana with food, brew with tea or placing marijuana-infused tincture or hash oil capsule under the tongue.[2] The effects of the drug is felt immediately when it is smoked, however when the drug is ingested it can take up to 90 minutes to feel the effect. This effect can last from 2 to 6 hours depending on the dosage and the person. When taken in high doses, high anxiety, delusions, paranoia, and hallucinations is often experienced.[4] Applying marijuana cream/lotion directly on the skin is known as tropical delivery. It has proven that reapplying marijuana cream/lotion frequently can help to relieve the arthritis pain. Transdermal patches can also be used in this case to deliver the correct dose of the medication to the affected area. It is very important to choose the correct delivery method and the dose for a given situation as the impact varies accordingly.[5]

Composition of marijuana

The composition of marijuana consists of more than 500 different compounds, and they can be categorized into four main groups. They are

cannabinoids, terpenoids, flavonoids and omega fatty acids. Terpenoids are mostly responsible for the unique aroma of cannabis. Studies have discovered that it is accountable for a variety of physiological effects when consumed, such as, rapid heartbeat, breathing problems and respiratory allergies when smoked as well as some unique therapeutic properties.[6] Some examples for terpenoids that are present in cannabis are myrcene, limonene, α-pinene and linalool. Flavonoids present in cannabis generally provide the pigmentation. However, these flavonoids have also been studied for anti-inflammatory, antioxidant and anti-carcinogenic properties. Apigenin, luteolin, kaempferol, quercetin, cannflavin A and cannflavin B can be named as few of the most common compounds that can be isolated from the cannabis plant.[7]

The most distinctive category that can be only found in cannabis is cannabinoids. There are over 140 cannabinoids isolated so far and the most popular cannabinoid is delta-9-tetrahydrocannabinol, commonly known as THC. This is the compound which is responsible for the "high" that most people use it for.[7] This is a psychoactive compound which directly affect the mood, emotion, and the perception of a person when it is ingested or smoked. However, THC is also studied for its strong anti-inflammatory activity, neuro-antioxidative activity (protects nervous tissue) and antispasmodic (relieves spasms) effects. The psychoactive component, THC, is formed due to decarboxylation of tetrahydrocannabinolic acid (THCA) (Figure 2) which is present in the plant. This conversion mainly takes place upon heating. Therefore, the raw form of cannabis is not psychoactive as the cannabinoids are in the form of carboxylic acids.[8, 9]

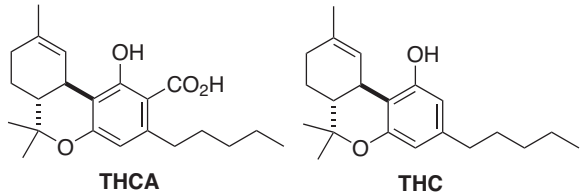

Figure 2: Structures of THCA and THC.

Cannabidiol is another cannabinoid present in cannabis, which is commonly known as CBD (Figure 3). This is a non-psychoactive compound that is used for its medical properties such as treating depression and anxiety, improving sleep, and improving overall mood. CBDs were a mainstream topic in the society after Dr. Sanjay Gupta announced about a special cannabis treatment on children with severe seizure disorders on a CNN special report in 2013.[11] CBD can also minimize the adverse effects that can caused by THC.[10]

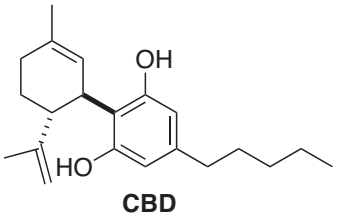

Figure 3: Structure of CBD.

Studies done during the past two decades in the USA has discovered that the "feral" cannabis which grows in the wild has approximately similar levels of THC and CBD while the "street" cannabis contain THC levels that are 10 to100 times greater than that of CBD. Decades of illegal breeding of marijuana for recreational use have drastically increased the levels of THC levels in marijuana that may cause potential health risks, such as cognitive and psychiatric disorders to its long-term users.[12] All the cannabinoids present in the cannabis plant are lipid soluble. This allows the drug to stay in the body for longer periods even after the effect of the drug wear offs. Therefore, the main psychoactive compound, THC can be detected in the body even several weeks after marijuana usage, depending on the sensitivity of the test taken.[13]

Apart from THC and CBD, most abundant cannabinoids that can be found in the cannabis plant are cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), delta-8-tetrahydrocannabinol (delta-8-THC), delta-9-tetrahydrocannabivarin (THCV), cannabivarin (CBV) and cannabidivarin (CBDV). The structures of the cannabinoids are shown in Figure 4. However, according to a very interesting study conducted by Dr. Ethan Russo, isolating a few abundant compounds separately from the plant and using them for its medicinal purpose does not work much as all these compounds have to work together to give the desired therapeutic effect. According to him even a little amount of terpene can make a significant difference in 1:1 THC:CBD ratio and this theory is commonly referred to as "entourage effect".[14]

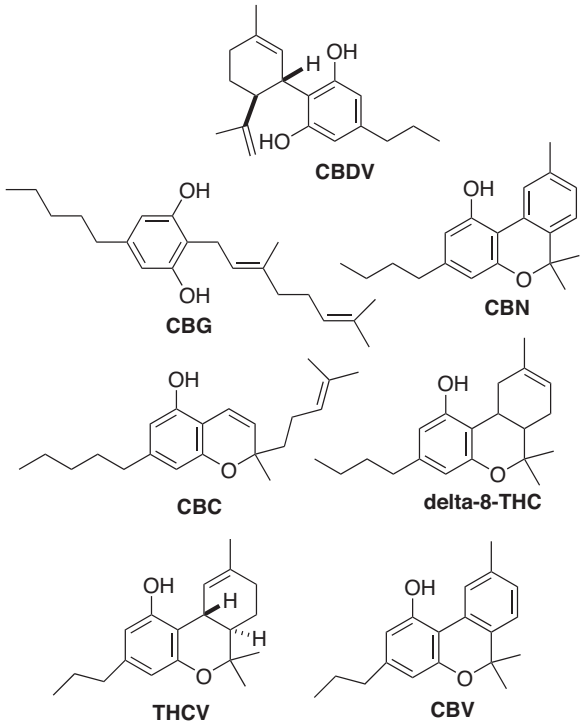

Figure 4: Structures of CBG, CBN, CBC, delta-8-THC, THCV, CBV and CBDV

How does marijuana affect the brain?

There are mainly two types of cannabinoid receptors named CB1 receptors and CB2 receptors. Both receptor types are G protein coupled receptors. CB1 receptors are found throughout the nervous system while CB2 receptors are primarily found in immune cells. THC found in marijuana acts as a partial agonist at cannabinoid receptors, which means, THC that binds to these receptors can generate a response that is a fraction of what other substances that binds to the receptors can generate.[15] Activation of CB1 can inhibit the enzyme adenylate cyclase. This enzyme is responsible of the conversion of adenosine triphosphate (ATP) to cAMP which plays an important role in cellular processes. Therefore, inhibiting adenylate cyclase results in low production of cAMP that leads to slow cellular responses and interrupting signaling pathways. THC interacts with other targets as well, but the main psychoactive effect of THC comes from the interaction with CB1 receptors.[16]

One of the main ways CBD affect the brain is by inhibiting the enzyme that blocks the formation of a chemical called "anandamide". The word anandamide comes from "Ananda", which is a Sanskrit word for happiness. Higher levels of this chemical help to improve the overall mood of a person by improving sleeping disorders, anxiety issues and the immune system related issues. By inhibiting the enzyme that blocks the production of anandamide, CBD contributes to increase the level of anandamide.[10] Anandamide also function as neurotransmitters and binds to cannabinoid receptors to activate them. Anandamide and THC has a very similar chemical structure (Figure 5). Therefore, the body often recognize THC as anandamide. This can alter various mental and physical functions in the body and disrupt normal brain function.[17] Activation of CB1 receptors in different areas of the brain may lead to different effects of THC in the body and the full extension of the mechanism of action is not fully understood yet. For example, CB1 receptors in cortex and hippocampus may be involved in perceptual and cognitive effects while the stimulation of CB1 receptors in the spinal cord and brainstem may be involved in analgesic effects. Also, the CB1 receptors in basal ganglia and cerebellum may be involved in sedation and effect on movement.[16]

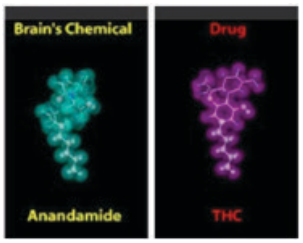

Figure 5: Structure of Anandamide and THC.[17]

Even though CBD is not studied to have psychoactive effects, it does interact with the nervous system to modulate the effects of THC. CBD also binds with CB1 receptors that are expressed in the nervous system. But instead of activating it, CBD binds to the receptor to reduce the chances of THC to bind with it. This type of action is known as a negative allosteric modulation and it helps to reduce the adverse effects of THC on the brain.[15] The amount of THC in marijuana, in other words, the strength of THC is not the only factor that impacts the brain. Age of first use, frequency of the use and also whether other substances were used with the marijuana also affects the brain function.[18,19]

Long term use of cannabis can lead to addiction like many other psychoactive drugs. It has been discovered that one out of every six people who has

used cannabis throughout their adulthood will develop a cannabis dependency and 9% of the people who has used cannabis end up been addicted to cannabis.[13] In addition to addiction, long term use of cannabis can also lead to psychiatric illnesses such as bipolar disorder and schizophrenia.[20] Regular users can often suffer from impaired attention, distorted short term memory and interruption in psychomotor function which can affect your day to day life. THC is considered as the main cause for marijuana addiction due to its ability to induce dopamine release in the brain.[15] Two longitudinal studies done over an extended period of time have also concluded that the magnitude of the functional impairment in cognitive abilities caused by using marijuana depends on the age of first use, how much and how long he or she have been using it for.[21] As people age, they lose their ability to learn new information as they lose neurons in the hippocampus. However, a report published in India in 2023 revealed that rats who got exposed to THC every day for 8 months (approximately 30% of their life span) have shown an increase rate of nerve cell loss at 11-12 months, that is equivalent to rats that are twice their age whom were unexposed to THC.[17] According to this study, getting exposed to THC regularly has aged the brain of mice faster than the healthy mice whom were not exposed to THC.

Some research also reveal that marijuana addiction can lead to use of other licit and illicit substances and push to develop an addiction to other substances such as alcohol, cocaine and tobacco.[22] A study conducted by the National Epidemiological Study of Alcohol Use and Related Disorders, found out that adults who used marijuana were more likely to develop an alcohol use disorder within 3 years than adults who did not use marijuana. Marijuana is also linked with substance use disorders such as nicotine addiction.[23]

Adversity of marijuana withdrawal and treatments

Typically, the withdrawal symptoms of an addicted marijuana user can appear within 1-2 days and can last up to 2 weeks.[24] During this period, negative effects such as anxiety, irritability, lack of motivation, low appetite and insomnia can be observed. Due to low levels of dopamine, chronic marijuana users between the ages of 13-23 can show adverse withdrawal symptoms such as decline in verbal memory, working memory and decision making. This can directly affect the development of the brain in young adults as it can alter the striatum of the brain. Chronic marijuana abusers can also alter the prefrontal cortex structure of the brain that leads to long lasting cognitive defects.[15] It has also reported that cannabis withdrawal can also disrupt the reward processing and reward-seeking behavior due to the down regulation of CB1 receptors.[13]

Although, marijuana use disorder is very much like other substance use disorders, the severity of its long-term clinical outcomes are very less. According to data published in 2016, adults that pursue treatment for marijuana use disorder have used marijuana daily for more than 10 years with more than 6 failed attempts to quit.[25] However, FDA has not yet approved any medication for people with marijuana use disorders. Studies have revealed that standard treatments which involve behavioral therapy has been effective to reduce the use of marijuana among addicted patients. Treatments such as cognitive-behavioral therapy, contingency management and motivational enhancement therapy have shown promising results in treating marijuana addicts so far.[26]

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