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Why smoking pot feels so good: New neuroscience explains marijuana and the brain

Might marijuana actually prevent age-related memory loss? New science suggests we have lots to learn about pot

James Franco and Seth Rogen in "Pineapple Express"

Excerpted from "Your Brain on Food: How Chemicals Control Your Thoughts and Feelings"

What drug is enjoyable and, under some circumstances, might actually be good for your brain? Can smoking this substance prevent age-related memory loss, for example? To answer these and similar questions, I turn now to a neurotransmitter system in the brain that was discovered through the use of one of the most common drugs in our history. This system may not have the most familiar of names — **endogenous cannabinoid neurotransmitter** — but the drug that tells us most about its function is certainly a household word: **marijuana**. Indeed, few drugs have the kind of colorful history that marijuana has achieved. Thus, before examining the neurotransmitter that it affects, let's look briefly at the story of the drug itself.

Dope and a rope

Among species of marijuana plants, ***Cannabis indica*** is the one grown principally for its psychoactive resins. It is likely a shorter, bushier version of the ***Cannabis sativa***, which is used primarily for its fibers to make rope. Both plants, like catnip, contain active ingredients belonging to a **family of compounds called terpenes**, of which the primary psychoactive terpene is thought to be concentrated in the plants' resin as **delta-9 tetrahydrocannabinol (THC)**. Initially investigated more than 100 years ago by two chemists, the Smith Brothers (William and Andrew) of later cough-drop fame, the plants **contain approximately 50 cannabinoid-based compounds**, with 4 major cannabinoids: trans-delta-9-THC and delta-8-THC, cannabidiol (the second most abundant psychoactive ingredient after THC), and cannabinol, which may be a decomposition product of THC that accumulates as cannabis samples age. After ingestion, the trans-delta-9-THC is converted in the liver to 11-hydroxy THC, which is equally potent and psychoactive.

Probably the **oldest reference** to the cannabis plant, in a pharmacy book from **2737 B.C.**, is related to its use as a medicine. The Chinese emperor Shen Nung (the Divine Farmer) referred to it as the **"liberator of sin"** and recommended it for the treatment of "female weakness," gout, rheumatism, malaria, constipation, and absent-mindedness. By 1000 B.C., its medicinal use, as indicated by available writings, had spread to India; by 500 B.C., it was **familiar to the ancient Greeks.**

The earliest reference to the use of cannabis as an inebriant was in **430 B.C., when the Greek historian Herodotus of Halicarnassus wrote that the Scythians burned the seeds and inhaled the smoke to induce intoxication during funerals.** The plant is also mentioned several times (as "kaneh-bosem,") in the Old Testament (as Yahweh's instruction to Moses in Exodus 30:23) as a bartering material, incense, and an ingredient in holy anointing oil; it was likely used by the high priests of the temple as well as by Jesus. At that time in history, the word *messiah* simply meant "the anointed one." Use of the plant as an inebriant spread to the Muslim world and North Africa by 1000 A.D. and became epidemic by the 12th century. The exploring Spaniards likely brought kanehbos, by now probably pronounced as cannabis, to the New World in about 1545.

Meanwhile, let's not forget that other, more humdrum role that cannabis has played in history. **English settlers brought it, as well as tobacco, to Jamestown, Virginia, by 1611** and used its fibers to make rope. In the 1700s, George Washington grew cannabis on his farm and, according to entries in his diary, maintained a keen interest in cultivating better strains of the plant, evidently for the purpose of producing a better quality of rope. In 1942, the U.S. government made a number of movie-shorts aimed at encouraging farmers to plant hemp, or cannabis, for wartime use as rope. Other rather famous historical uses of **cannabis fiber are said to include Chinese paper, the ropes and sails on Christopher Columbus's ships, the Declaration of Independence, World War II parachutes, and the first Levi jeans.**

Today, when most people hear the term *marijuana*, they think of the leafy material from ***C. indica*** that is generally smoked. It contains **2% to 5% THC. Sinsemilla or ganja, made from the unpollinated female cannabis plant, may contain up to 15% THC.** Hashish, which is actually the Arabic word for grass (which might explain the slang term for this plant), is made from a dried concentrate of the resin of cannabis flowers and contains about 8% to 14% THC. **Hashish oil typically has from 15% to 60% THC**, and bhang, a drink popular in India that is made of cannabis leaves, milk, sugar, and spices, has 2% to 5% THC. Kief (from the Arabic kaif meaning "pleasure, well-being") is made from the dried resin of *C. indica* and usually has very high THC levels. Budder is a processed and concentrated form of hashish oil that is reported to contain between 82% and 99% THC by weight. Given its potency and effectiveness, it probably takes a lot of bread to buy this budder.

Whatever its form, marijuana is today **categorized as a gateway drug for its role in leading users to try other illegal drugs**. Overall, statistics show that very few young people use other illegal drugs without first trying marijuana. But the majority of

marijuana users **(about 60%) do not go on to use any other illicit drugs.** By contrast, according to some statistics, **most users report having tried legal substances—cigarettes or beer—before trying marijuana**. Thus, tobacco and alcohol products could be considered gateway drugs as well. It's worth pointing out that that **alcohol is considered as addictive as heroin, and tobacco is considered as addictive as crack cocaine.**

What does marijuana do in the brain? It produces some **excitatory behavioral changes, including euphoria, but it is not generally regarded as a stimulant.** It can also produce **some sedative effects**, but not to the extent of a barbiturate or alcohol. It produces **mild analgesic effects** (pain relief) as well, but this action is not related pharmacologically to the pain-relieving effects of opiates or aspirin. Finally, marijuana **produces hallucinations at high doses**, but its structure does not resemble LSD or any other drug formally categorized as a hallucinogen. Thus, marijuana's effects on our body and brain are complex. Just how does it achieve these effects?

The very high potency and structure of the cannabinoids contained within the marijuana plant enable them to **cross the blood–brain barrier and bind to a receptor for the brain's very own endogenous cannabinoid neurotransmitter system.** If this were not true, then the marijuana plant would be popular only for its use in making rope, paper, and cloth. The **two currently identified neurotransmitter compounds** (and there are probably more) in this system are **anandamide**, from the Sanskrit word *ananda* meaning "bliss," and **2-AG (2-arachidonoyl-glycerol)**. Unlike the other neurotransmitters that I've discussed, **these two "endocannabinoids" are not stored in synaptic vesicles**.

Rather, they are **both produced within neurons and released to flow backward across the synapse to find their receptors,** designated as CB1 and CB2. There are **probably more of these CB receptors for marijuana in the human brain than for any other known neurotransmitter.** The great abundance of these receptors and their widespread location gives an indication of the importance of the endocannabinoid system in the regulation of the brain's normal functioning.

Let's take a look at **what these endocannabinoids do in the brain**, to gain some insight into the consequences of smoking (or eating) marijuana. For example, **anandamide inhibits the release of glutamate and acetylcholine within the cortex and hippocampus**, an action that may **underlie the ability of marijuana to impair one's capacity to form new memories when using the drug.** The presence of cannabinoid receptors in the parts of the brain that control movement may explain the stumbling behavior that some marijuana users experience. **Cannabinoid receptors greatly enhance the release of dopamine;** this action plays a critical role in the ability of marijuana to **produce euphoria.** Finally, stimulation of **cannabinoid receptors in the feeding centers of the hypothalamus may underlie the classic marijuana side effect known as the "munchies."**

This last effect coincidentally drew the attention of scientists who conducted a series of clinical trials using a drug that blocks the brain's cannabinoid receptors. Their hope was

that this drug's blocking action would **produce an "anti-munchies" effect**, thereby **reducing food consumption** and providing help to overweight patients. **At first, the drug worked fairly well. People reported being less attracted to eating. Unfortunately, they also became severely depressed.** What this discovery tells scientists is that **our endogenous cannabinoid system** is normally involved, either **directly or indirectly, in elevating or controlling our mood** and that antagonizing the cannabinoid receptors in the brain, as occurred with this novel drug, can produce some dangerous consequences.

In contrast, **stimulating the brain's cannabinoid receptors** may **offer protection from the consequences of stroke, chronic pain, and neuroinflammation.** Surprisingly, it may also **protect against some aspects of age-associated memory loss**. Ordinarily, we do not view marijuana as being good for our brain and certainly not for making memories. How could a drug that clearly impairs memory while people are under its sway protect their brains from the consequences of aging?

The answer likely has everything to do with the **way that young and old brains function** and the **age-related changes in the actions of the neurotransmitters acetylcholine and glutamate**. These *two neurotransmitters are involved in making new memories and destroying old or unnecessary ones*. **Early in life,** *this process of creation and destruction is in balance, and so interfering with it—which occurs when using marijuana— might impair memory.* **But later in life**, the roles of these neurotransmitters change in significant ways. In addition, the aged brain displays increasing evidence of inflammation and a dramatic decline in the production of new neurons, called neurogenesis. **Marijuana may offer protection in at least three different ways**: *by preventing the damaging actions of glutamate, by reducing brain inflammation, and by restoring neurogenesis.* Thus, later in life, marijuana might actually help your brain, rather than harm it. Research in my laboratory by Dr. Yannick Marchalant suggests that it takes very little marijuana to produce benefits in the older brain; his motto is **"a puff is enough."**The challenge for pharmacologists in the future will be to isolate the beneficial aspects of marijuana from its psychoactive effects, which themselves can be an additional burden to those suffering from the consequences of an aging brain.

Once again, the distribution of a neurotransmitter provides clues to its function in the brain. For example, **our brains' endogenous cannabinoid neurons are in the hypothalamus** feeding centers; when these receptors are stimulated, we feel hungry, and when they are blocked, we become less interested in eating. Cannabinoid neurons also **influence the function of our cortex and various limbic (emotion-controlling) regions;** when we stimulate these receptors, we impair higher cognitive functions as we experience euphoria, and when they are blocked, we feel depression. Because our brain appears to have a large number of different types of neurons that are affected by marijuana, a complete explanation of this drug's effects remains nearly impossible. **What seems clear, however, is that the endogenous cannabinoid neurotransmitters that our brain produces do not appear to transmit information per se but appear to modulate how other neurotransmitter systems function.** In this way, they act quite differently from the manner in which most other neurotransmitters behave.

Migraine sufferers have few options for reducing their headache pain, and most of the medications available have unpleasant side effects that limit their long-term usefulness. About **20 years ago a new class of drugs, the triptans**, was introduced as an effective and safe alternative treatment. This class of drug works effectively for most patients but must be taken at the first sign of a headache. **These drugs have their own unwanted side effects, such as feeling hot or cold, weak, or "strange" in some way.** The **strange feelings are often given the term *serotonin syndrome*** and also include changes in mental status. These changes in mental status can be quite significant in individuals who carry a genetic vulnerability, such as people with bipolar illness or schizophrenia. The *assumption has been that these drugs work by acting upon serotonin receptors, which leads to a constriction of cerebral blood vessels. This assumption may be incorrect.*

One potentially important mechanism that was initially published in 1987 described how migraine headaches developed in some people shortly after they abruptly discontinued their long-term marijuana use. The implication was that marijuana was preventing the onset of migraines in vulnerable individuals. In addition, marijuana has long been known to possess analgesic properties. Possibly, the marijuana was somehow masking the pain of the migraines. A recent publication from the University of California, San Francisco, has offered a fascinating explanation for why the use of both triptans and marijuana prevents migraine headaches.

Our brain's own endogenous marijuana-like chemicals produce analgesia by modulating the entry of pain signals into the brain at the level of our spinal cord. Future generations of pain relievers will likely be developed on the basis of this action of marijuana in the body. The advantage of targeting the endogenous marijuana system is that **only noxious or painful signals are blocked; normal touch sensation is normal.**

This recent study made two significant advances: *It confirmed the role of the endogenous marijuana neurotransmitter system as a potential target for treating migraines, and the results suggest that triptans may produce their migraine relief by activating the brain's own endogenous marijuana-like chemicals*. This study may lead to the development of more effective migraine prevention and treatment. The challenge will be to find a dose of marijuana that produces pain relief without disturbing normal cognitive function.

Marijuana for the treatment of psychic pain

The loss of someone you love hurts. Losing your job is painful. No one wants to be ignored because it brings on heartache and depression and possibly increases your chances of developing cancer or dementia. The field of psychoneuroimmunology has evolved to study the link between social and physical pain. Obviously, to anyone who has experienced any of these events in life, the **link between psychic and physical is quite real, and the symptoms are very difficult to treat.**

During the evolution of our brain, those areas that were once only responsible for experiencing the sensory component of pain slowly evolved to provide the sensations associated with the emotional components of pain and its experience. We now respond

with a psychic aching to social isolation that is often accompanied by a headache, nausea, depression, loss of appetite, and many other essential body functions. Recently, scientists speculated that **because these two systems overlap functionally and anatomically** in the brain, it **might be possible to reduce social pain by targeting the physical pain experience with common over-the-counter drugs.**

Two different types of **common analgesics, acetaminophen and ibuprofen** (i.e., Tylenol and Advil), are capable of **producing this combined benefit** by enhancing the action of the brain's endogenous marijuana neurotransmitters. A recent study demonstrated that regular marijuana use reduced the experience of low self-worth and the incidence of major depressive episodes in lonely people. This research supports the hypothesis that treating physical pain with simple over-the-counter drugs might lessen the psychic pain as well.

How are these simple over-the-counter drugs able to provide relief of psychic pain? They enhance the action of anandamide. Anandamide and the other marijuana-like chemicals in your brain are well known to control happiness and euphoria.
Once anandamide is released inside your brain it is rather quickly inactivated by specific enzymes. One of these enzymes is called cyclooxygenase (COX). Ibuprofen and acetaminophen inhibit the function of COX. Thus, taking these drugs may enhance the actions of anandamide and thereby mimic the effects of marijuana in your brain. Obviously, their action in the brain must be rather subtle; otherwise these products would no longer be so easily available. Ultimately, targeting the biological mechanisms underlying the symptoms of loneliness might only require a trip to your corner drugstore.