

## The Brain's Own Marijuana

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Marijuana is a drug with a mixed history. Mention it to one person, and it will conjure images of potheads lost in a spaced-out stupor. To another, it may represent relaxation, a slowing down of modern madness. To yet another, marijuana means hope for cancer patients suffering from the debilitating nausea of chemotherapy, or it is the promise of relief from chronic pain. The drug is all these things and more, for its history is a long one, spanning millennia and continents. It is also something everyone is familiar with, whether they know it or not. Everyone grows a form of the drug, regardless of their political leanings or recreational proclivities. That is because the brain makes its own marijuana, natural compounds called endocannabinoids (after the plant's formal name, *Cannabis sativa*).

The study of endocannabinoids in recent years has led to exciting discoveries. By examining these substances, researchers have exposed an entirely new signaling system in the brain: a way that nerve cells communicate that no one anticipated even 15 years ago. Fully understanding this signaling system could have far-reaching implications. The details appear to hold a key to devising treatments for anxiety, pain, nausea, obesity, brain injury and many other medical problems. Ultimately such treatments could be tailored precisely so that they would not initiate the unwanted side effects produced by marijuana itself.

### **A Checkered Past**

Marijuana and its various alter egos, such as bhang and hashish, are among the most widely used psychoactive drugs in the world. How the plant has been used varies by culture. The ancient Chinese knew of marijuana's pain-relieving and mind-altering effects, yet it was not widely employed for its psychoactive properties; instead it was cultivated as hemp for the manufacture of rope and fabric. Likewise, the ancient Greeks and Romans used hemp to make rope and sails. In some other places, however, marijuana's intoxicating properties became important. In India, for example, the plant was incorporated into religious rituals. During the Middle Ages, its use was common in Arab lands; in 15th-century Iraq it was used to treat epilepsy; in Egypt it was primarily consumed as an inebriant. After Napoleon's occupation of Egypt, Europeans began using the drug as an intoxicant. During the slave trade, it was transported from Africa to Mexico, the Caribbean and South America.

Marijuana gained a following in the U.S. only relatively recently. During the second half of the 19th century and the beginning of the 20th, cannabis was freely available without a

prescription for a wide range of ailments, including migraine and ulcers. Immigrants from Mexico introduced it as a recreational drug to New Orleans and other large cities, where it became popular among jazz musicians. By the 1930s it had fallen into disrepute, and an intense lobbying campaign demonized "reefer madness." In 1937 the U.S. Congress, against the advice of the American Medical Association, passed the Marijuana Tax Act, effectively banning use of the drug by making it expensive and difficult to obtain. Ever since, marijuana has remained one of the most controversial drugs in American society. Despite efforts to change its status, it remains federally classified as a Schedule 1 drug, along with heroin and LSD, considered dangerous and without utility.

Millions of people smoke or ingest marijuana for its intoxicating effects, which are subjective and often described as resembling an alcoholic "high." It is estimated that approximately 30 percent of the U.S. population older than 12 have tried marijuana, but only about 5 percent are current users. Large doses cause hallucinations in some individuals but simply trigger sleep in others. The weed impairs short-term memory and cognition and adversely affects motor coordination, although these setbacks seem to be reversible once the drug has been purged from the body. Smoking marijuana also poses health risks that resemble those of smoking tobacco.

On the other hand, the drug has clear medicinal benefits. Marijuana alleviates pain and anxiety. It can prevent the death of injured neurons. It suppresses vomiting and enhances appetite--useful features for patients suffering the severe weight loss that can result from chemotherapy.

### **Finding the Responsible Agent**

Figuring out how the drug exerts these myriad effects has taken a long time. In 1964, after nearly a century of work by many individuals, Raphael Mechoulam of the Hebrew University in Jerusalem identified delta-9-tetrahydrocannabinol (THC) as the compound that accounts for virtually all the pharmacological activity of marijuana. The next step was to identify the receptor or receptors to which THC was binding.

Receptors are small proteins embedded in the membranes of all cells, including neurons, and when specific molecules bind to them--fitting like one puzzle piece into another--changes in the cell occur. Some receptors have water-filled pores or channels that permit chemical ions to pass into or out of the cell. These kinds of receptors work by changing the relative voltage inside and outside the cell. Other receptors are not channels but are coupled to specialized proteins called G-proteins. These G-protein-coupled receptors represent a large family that set in motion a variety of biochemical signaling cascades within cells, often resulting in changes in ion channels.

In 1988 Allyn C. Howlett and her colleagues at St. Louis University attached a radioactive tag to a chemical derivative of THC and watched where the compound went in rats' brains. They discovered that it attached itself to what came to be called the cannabinoid receptor, also known as CB1. Based on this finding and on work by Miles Herkenham of the National Institutes of Health, Lisa Matsuda, also at the NIH, cloned the CB1 receptor. The importance of CB1 in the action of THC was proved when two

researchers working independently--Catherine Ledent of the Free University of Brussels and Andreas Zimmer of the Laboratory of Molecular Neurobiology at the University of Bonn--bred mice that lacked this receptor. Both investigators found that THC had virtually no effect when administered to such a mouse: the compound had nowhere to bind and hence could not trigger any activity. (Another cannabinoid receptor, CB2, was later discovered; it operates only outside the brain and spinal cord and is involved with the immune system.)

As researchers continued to study CB1, they learned that it was one of the most abundant G-protein coupled receptors in the brain. It has its highest densities in the cerebral cortex, hippocampus, hypothalamus, cerebellum, basal ganglia, brain stem, spinal cord and amygdala. This distribution explains marijuana's diverse effects. Its psychoactive power comes from its action in the cerebral cortex. Memory impairment is rooted in the hippocampus, a structure essential for memory formation. The drug causes motor dysfunction by acting on movement control centers of the brain. In the brain stem and spinal cord, it brings about the reduction of pain; the brain stem also controls the vomiting reflex. The hypothalamus is involved in appetite, the amygdala in emotional responses. Marijuana clearly does so much because it acts everywhere.

Over time, details about CB1's neuronal location emerged as well. Elegant studies by Tamás F. Freund of the Institute of Experimental Medicine at the Hungarian Academy of Sciences in Budapest and Kenneth P. Mackie of the University of Washington revealed that the cannabinoid receptor occurred only on certain neurons and in very specific positions on those neurons. It was densely packed on neurons that released GABA (gamma-aminobutyric acid), which is the brain's main inhibitory neurotransmitter (it tells recipient neurons to stop firing). CB1 also sat near the synapse, the contact point between two neurons. This placement suggested that the cannabinoid receptor was somehow involved with signal transmission across GABA-using synapses. But why would the brain's signaling system include a receptor for something produced by a plant?

### **The Lesson of Opium**

The same question had arisen in the 1970s about morphine, a compound isolated from the poppy and found to bind to so-called opiate receptors in the brain. Scientists finally discovered that people make their own opioids--the enkephalins and endorphins. Morphine simply hijacks the receptors for the brain's opioids.

It seemed likely that something similar was happening with THC and the cannabinoid receptor. In 1992, 28 years after he identified THC, Mechoulam discovered a small fatty acid produced in the brain that binds to CB1 and that mimics all the activities of marijuana. He named it anandamide, after the Sanskrit word ananda, "bliss." Subsequently, Daniele Piomelli and Nephi Stella of the University of California at Irvine discovered that another lipid, 2-arachidonoyl glycerol (2-AG), is even more abundant in certain brain regions than anandamide is. Together the two compounds are considered the major endogenous cannabinoids, or endocannabinoids. (Recently investigators have identified what look like other endogenous cannabinoids, but their roles are uncertain.) The two cannabinoid receptors clearly evolved along with endocannabinoids as part of

natural cellular communication systems. Marijuana happens to resemble the endocannabinoids enough to activate cannabinoid receptors.

Conventional neurotransmitters are water-soluble and are stored in high concentrations in little packets, or vesicles, as they wait to be released by a neuron. When a neuron fires, sending an electrical signal down its axon to its tips (presynaptic terminals), neurotransmitters released from vesicles cross a tiny intercellular space (the synaptic cleft) to receptors on the surface of a recipient, or postsynaptic, neuron. In contrast, endocannabinoids are fats and are not stored but rather are rapidly synthesized from components of the cell membrane. They are then released from places all over the cells when levels of calcium rise inside the neuron or when certain G-protein-coupled receptors are activated.

As unconventional neurotransmitters, canna-bin-oids presented a mystery, and for several years no one could figure out what role they played in the brain. Then, in the early 1990s, the answer emerged in a somewhat roundabout fashion. Scientists (including one of us, Alger, and his colleague at the University of Maryland School of Medicine, Thomas A. Pitler) found something unusual when studying pyramidal neurons, the principal cells of the hippocampus. After calcium concentrations inside the cells rose for a short time, incoming inhibitory signals in the form of GABA arriving from other neurons declined.

At the same time, Alain Marty, now at the Laboratory of Brain Physiology at the René Descartes University in Paris, and his colleagues saw the same action in nerve cells from the cerebellum. These were unexpected observations, because they suggested that receiving cells were somehow affecting transmitting cells and, as far as anyone knew, signals in mature brains flowed across synapses in one way only: from the presynaptic cell to the postsynaptic one.

### **A New Signaling System**

It seemed possible that a new kind of neuronal communication had been discovered, and so researchers set out to understand this phenomenon. They dubbed the new activity DSI, for depolarization-induced suppression of inhibition. For DSI to have occurred, some unknown messenger must have traveled from the postsynaptic cell to the presynaptic GABA-releasing one and somehow shut off the neurotransmitter's release.

Such backward, or "retrograde," signaling was known to occur only during the development of the nervous system. If it were also involved in interactions among adult neurons, that would be an intriguing finding--a sign that perhaps other processes in the brain involved retrograde transmission as well. Retrograde signaling might facilitate types of neuronal information processing that were difficult or impossible to accomplish with conventional synaptic transmission. Therefore, it was important to learn the properties of the retrograde signal. Yet its identity remained elusive. Over the years, countless molecules were proposed. None of them worked as predicted.

Then, in 2001, one of us (Nicoll) and his colleague at the University of California at San Francisco, Rachel I. Wilson--and at the same time, but independently, a group led by

Masanobu Kano of Kanazawa University in Japan--reported that an endocannabinoid, probably 2-AG, perfectly fit the criteria for the unknown messenger. Both groups found that a drug blocking cannabinoid receptors on presynaptic cells prevents DSI and, conversely, that drugs activating CB1 mimic DSI. They soon showed, as did others, that mice lacking cannabinoid receptors are incapable of generating DSI. The fact that the receptors are located on the presynaptic terminals of GABA neurons now made perfect sense. The receptors were poised to detect and respond to endocannabinoids released from the membranes of nearby postsynaptic cells.

Over time, DSI proved to be an important aspect of brain activity. Temporarily dampening inhibition enhances a form of learning called long-term potentiation--the process by which information is stored through the strengthening of synapses. Such storage and information transfer often involves small groups of neurons rather than large neuronal populations, and endocannabinoids are well suited to acting on these small assemblages. As fat-soluble molecules, they do not diffuse over great distances in the watery extracellular environment of the brain. Avid uptake and degradation mechanisms help to ensure that they act in a confined space for a limited period. Thus, DSI, which is a short-lived local effect, enables individual neurons to disconnect briefly from their neighbors and encode information.

A host of other findings filled in additional gaps in understanding about the cellular function of endocannabinoids. Researchers showed that when these neurotransmitters lock onto CB1 they can in some cases block presynaptic cells from releasing excitatory neurotransmitters. As Wade G. Regehr of Harvard University and Anatol C. Kreitzer, now at Stanford University, found in the cerebellum, endocannabinoids located on excitatory nerve terminals aid in the regulation of the massive numbers of synapses involved in coordinated motor control and sensory integration. This involvement explains, in part, the slight motor dysfunction and altered sensory perceptions often associated with smoking marijuana.

Recent discoveries have also begun to precisely link the neuronal effects of endocannabinoids to their behavioral and physiological effects. Scientists investigating the basis of anxiety commonly begin by training rodents to associate a particular signal with something that frightens them. They often administer a brief mild shock to the feet at the same time that they generate a sound. After a while the animal will freeze in anticipation of the shock if it hears the sound. If the sound is repeatedly played without the shock, however, the animal stops being afraid when it hears the sound--that is, it unlearns the fear conditioning, a process called extinction. In 2003 Giovanni Marsicano of the Max Planck Institute of Psychiatry in Munich and his co-workers showed that mice lacking normal CB1 readily learn to fear the shock-related sound, but in contrast to animals with intact CB1, they fail to lose their fear of the sound when it stops being coupled with the shock.

The results indicate that endocannabinoids are important in extinguishing the bad feelings and pain triggered by reminders of past experiences. The discoveries raise the possibility that abnormally low numbers of cannabinoid receptors or the faulty release of

endogenous cannabinoids are involved in post-traumatic stress syndrome, phobias and certain forms of chronic pain. This suggestion fits with the fact that some people smoke marijuana to decrease their anxiety. It is also conceivable, though far from proved, that chemical mimics of these natural substances could allow us to put the past behind us when signals that we have learned to associate with certain dangers no longer have meaning in the real world.

### **Devising New Therapies**

The repertoire of the brain's own marijuana has not been fully revealed, but the insights about endocannabinoids have begun helping researchers design therapies to harness the medicinal properties of the plant. Several synthetic THC analogues are already commercially available, such as nabilone and dronabinol. They combat the nausea brought on by chemotherapy; dronabinol also stimulates appetite in AIDS patients. Other cannabinoids relieve pain in myriad illnesses and disorders. In addition, a CB1 antagonist--a compound that blocks the receptor and renders it impotent--has worked in some clinical trials to treat obesity. But though promising, these drugs all have multiple effects because they are not specific to the region that needs to be targeted. Instead they go everywhere, causing such adverse reactions as dizziness, sleepiness, problems of concentration and thinking abnormalities.

One way around these problems is to enhance the role of the body's own endocannabinoids. If this strategy is successful, endocannabinoids could be called forth only under the circumstances and in the locations in which they are needed, thus avoiding the risks associated with widespread and indiscriminant activation of cannabinoid receptors. To do this, Piomelli and his colleagues are developing drugs that prevent the endocannabinoid anandamide from being degraded after it is released from cells. Because it is no longer broken down quickly, its anxiety-relieving effects last longer.

Anandamide seems to be the most abundant endocannabinoid in some brain regions, whereas 2-AG dominates in others. A better understanding of the chemical pathways that produce each endocannabinoid could lead to drugs that would affect only one or the other. In addition, we know that endocannabinoids are not produced when neurons fire just once but only when they fire five or even 10 times in a row. Drugs could be developed that would alter the firing rate and hence endocannabinoid release. A precedent for this idea is the class of anticonvulsant agents that suppress the neuronal hyperactivity underlying epileptic seizures but do not affect normal activity.

Finally, indirect approaches could target processes that themselves regulate endocannabinoids. Dopamine is well known as the neurotransmitter lost in Parkinson's disease, but it is also a key player in the brain's reward systems. Many pleasurable or addictive drugs, including nicotine and morphine, produce their effects in part by causing dopamine to be released in several brain centers. It turns out that dopamine can cause the release of endocannabinoids, and various research teams have found that two other neurotransmitters, glutamate and acetylcholine, also initiate endocannabinoid synthesis and release. Indeed, endocannabinoids may be a source of effects previously attributed solely to these neurotransmitters. Rather than targeting the endocannabinoid system

directly, drugs could be designed to affect the conventional neurotransmitters. Regional differences in neurotransmitter systems could be exploited to ensure that endocannabinoids would be released only where they were needed and in appropriate amounts.

In a remarkable way, the effects of marijuana have led to the still unfolding story of the endocannabinoids. The receptor CB1 seems to be present in all vertebrate species, suggesting that systems employing the brain's own marijuana have been in existence for about 500 million years. During that time, endocannabinoids have been adapted to serve numerous, often subtle, functions. We have learned that they do not affect the development of fear, but the forgetting of fear; they do not alter the ability to eat, but the desirability of the food, and so on. Their presence in parts of the brain associated with complex motor behavior, cognition, learning and memory implies that much remains to be discovered about the uses to which evolution has put these interesting messengers.

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