Editor’s Note: The endogenous cannabinoid system—named for the plant that led to its discovery—is one of the most important physiologic systems involved in establishing and maintaining human health. Endocannabinoids and their receptors are found throughout the body: in the brain, organs, connective tissues, glands, and immune cells. With its complex actions in our immune system, nervous system, and virtually all of the body’s organs, the endocannabinoids are literally a bridge between body and mind. By understanding this system, we begin to see a mechanism that could connect brain activity and states of physical health and disease.
Cannabis, derived from a plant and one of the oldest known drugs, has remained a source of controversy throughout its history. From debates on its medicinal value and legalization to concerns about dependency and schizophrenia, cannabis (marijuana, pot, hashish, bhang, etc.) is a hot button for politicians and pundits alike. Fundamental to understanding these discussions is how cannabis affects the mind and body, as well as the body’s cells and systems. How can something that stimulates appetite also be great for relieving pain, nausea, seizures, and anxiety? Whether its leaves and buds are smoked, baked into pastries, processed into pills, or steeped as tea and sipped, cannabis affects us in ways that are sometimes hard to define. Not only are its many facets an intrinsically fascinating topic, but because they touch on so many parts of the brain and the body, their medical, ethical, and legal ramifications are vast.

The intercellular signaling molecules, their receptors, and synthetic and degradative enzymes from which cannabis gets its powers had been in place for millions of years by the time humans began burning the plants and inhaling the smoke. Despite records going back 4,700 years that document medicinal uses of cannabis, no one knew how it worked until 1964. That was when Yechiel Gaoni and Raphael Mechoulam\(^1\) reported that the main active component of cannabis is tetrahydrocannabinol (THC). THC, referred to as a “cannabinoid” (like the dozens of other unique constituents of cannabis), acts on the brain by muscling in on the intrinsic neuronal signaling system, mimicking a key natural player, and basically hijacking it for reasons best known to the plants. Since the time when exogenous cannabinoids revealed their existence, the entire natural complex came to be called the “endogenous cannabinoid system,” or “endocannabinoid system” (ECS).

THC is a lipid, but in 1964, known or suspected neurotransmitters and neuromodulators were water-soluble molecules—peptides, amino acids, or amines—not lipids. Ordinary neuroactive agents interact with cells by binding to specific proteinaceous receptor molecules that are part of the cell surface. Each receptor has an intricate structural pocket into which a particular neurotransmitter fits. The interaction triggers the biochemical and biophysical reactions that affect the physiological properties of the cell. Lipids avoid water, and individual lipid molecules might simply drift freely around in a compatible lipophilic environment, such as the cell surface membrane, without having much to do with proteins. How could they influence neuronal behavior?
The best scientific guess at the time was that molecules such as THC would owe their psychotropic actions to “membrane fluidizing” properties, a vague notion that would not explain specificity of action, among other things. Nevertheless, strong evidence that THC and similar synthetic molecules could bind tightly to specific sites in the brain emerged, implying that THC does indeed work through true receptors. This hypothesis was confirmed in 1990 with the isolation and cloning of the first cannabinoid receptor, CB1, and later of CB2.

In the central nervous system (CNS), CB1 is by far the predominant form, although it also exists outside the CNS; CB2 is primarily found outside the CNS, and is associated with the immune system. Both receptor subtypes are 7-transmembrane domain macromolecules of the “G-protein-coupled” class. Unexpectedly, CB1 turned out to be one of the most abundant G-protein-coupled receptors in the brain. It was immediately obvious that CB1 and CB2 must partner with an endogenous ligand, a natural agent for which they would normally act as the proper receptors. They did not evolve to react with rarely ingested, plant-derived chemicals. Indeed, Mechoulam’s group isolated an arachidonic acid derivative (N-arachidonoyl ethanolamide, “anandamide”) that activated CB1, and a second endogenous CB1 ligand two-arachidonolyl glycerol (2-AG) was later discovered.

These endocannabinoids are the major physiological activators of CB1 and CB2, yet they are not standard neurotransmitters. For one thing, like THC, they are lipids, and brain cells, mainly neurons, are surrounded by an aqueous solution, an inhospitable environment for an intercellular lipid messenger. More surprisingly, endocannabinoids go against the flow of typical chemical synaptic signaling. A neuron that releases a chemical neurotransmitter (say, GABA or glutamate) is designated as “pre-synaptic;” the target neuron that expresses receptors for that neurotransmitter is “post-synaptic.” Endocannabinoids, however, are synthesized and released from post-synaptic cells, and travel backward (in the “retrograde” direction) across the synapse, where they encounter CB1s located on adjacent nerve terminals. Physiologically, CB1Rs act as communications traffic cops. Precisely positioned in synaptic regions, they inhibit the release of many excitatory and inhibitory neurotransmitters. Thus, by releasing endocannabinoids, postsynaptic target cells can influence their own incoming synaptic signals.

CB1 is densely located in the neocortex, hippocampus, basal ganglia, amygdala, striatum, cerebellum, and hypothalamus. These major brain regions mediate a wide variety of high-order
behavioral functions, including learning and memory, executive function decision making, sensory and motor responsiveness, and emotional reactions, as well as feeding and other homeostatic processes. Within neuronal circuits, suppression of excitatory transmitter release tends to dampen excitation, while suppression of inhibitory transmitter release favors neuronal network excitation. Given the enormous complexity of the brain, the endocannabinoid system could affect behavior in an almost limitless number of ways: simple generalizations of what will happen when CB1 receptors are globally turned on or off are not feasible. The challenge for developers of cannabinoid-based medicines is to find beneficial ways to exploit this powerful yet convoluted feedback system.

From a therapeutic point of view, the near ubiquity of the endocannabinoid system has good news/bad news implications. Good news because it offers explanatory power—the ability to make sense of numerous yet quite different aspects of neural processing involving the endocannabinoid system in normal brains, and conversely, to offer insight into a variety of maladies that accompany its dysfunction. Bad news because wide heterogeneous dispersion greatly complicates the task of targeting this system for specific therapeutic purposes. Side effects are therefore common and problematic.

**CB1 and Obesity**

Obesity is a serious worldwide health concern. An attempt to develop an endocannabinoid system–based strategy to solve it provides a textbook example of the promise and the problems involved. The feeding control centers in the hypothalamus express high concentrations of CB1. These receptors are responsible for “the munchies,” the craving for food that is stimulated by cannabis use. But they also prompt the normal desire to eat. Preventing the activation of hypothalamic CB1s should decrease eating. In addition, CB1 receptors outside the brain regulate energy metabolism in the liver and fat tissue, and pharmacologically blocking these peripheral receptors in animal studies results in less body weight gain even when the same amount of food was eaten. Researchers at the pharmaceutical company Sanofi-Aventis gave the CB1 antagonist rimonabant to obese individuals in multi-year, multi-thousand-patient trials and obtained stunning results. The drug worked brilliantly; patients lost weight and girth. Negative side effects (depression, anxiety, and nausea) occurred in 10 percent of the users, but they were not life-threatening and the risks were deemed worth the rewards. Rimonabant (marketed as “Acomplia®” among other names)
became readily available in 56 countries in 2006, and Sanofi’s stock soared. When approached to approve sale in the United States, however, the Federal Drug Administration (FDA) was skeptical and asked for more information about the drug’s performance after the clinical trials had ended.

The trials had excluded people who were susceptible to psychiatric illness, including depression. What was the experience like in the real world, where many obese patients also suffer from mental disturbances? The answer was alarming; the incidence of serious depression, including suicidal ideation, bouts of nausea, stress, and anxiety was markedly higher than in the trials. The beneficial effects of rimonabant and its downsides both arose from the same source. Blocking CB1 in the hypothalamus was beneficial because it diminished the desire to eat, but the drug, which was given orally, blocked CB1 throughout the body, including in those brain regions where the endocannabinoid system regulates emotion and vomiting reflexes, among others. Which effects predominated was a matter of individual variation, and it had to be assumed that widespread use of rimonabant would put many people at risk for serious adverse consequences. The FDA disapproved its distribution in the United States, and as reports of bad outcomes increased among patients in other countries, it was soon withdrawn from the market. As a result, Sanofi’s stock came back to earth.

**Inhibit vs. Stimulate**

Some conditions, such as chronic pain, spasticity, anxiety, and the wasting syndrome associated with chemotherapy and AIDS, can be alleviated by cannabinoids, and therefore therapeutic approaches would involve activating, not inhibiting, CB1. For example, people self-medicate with cannabis to relieve anxiety. The endocannabinoid system helps us deal with traumatic life experiences as a part of a normal coping mechanism—to forget it and leave the past behind. Neuroscientists use animal models, often the “fear conditioning” test, to investigate the development of anxiety. This is a Pavlovian training procedure in which a mildly unpleasant stimulus (a brief electric shock to the wire floor grid on which a rat or mouse is standing) is paired with a neutral tone, audible though not loud. The shock causes the animals to freeze in position—the typical response of small rodents to threatening stimuli. When the tone is sounded alone, it elicits a bit of curiosity, then soon is ignored. When the tone repeatedly precedes and accompanies the foot
shock, the animal comes to recognize it as a bad omen and eventually responds when the tone first sounds even when the shock no longer occurs. The animal has acquired conditioned fear.

Normal coping includes dissipation of the bad memories evoked by the tone (actually learning that the tone is no longer threatening), a process called “extinction,” which enables animals to cease paying the high costs of pointless responding. Mice genetically engineered so that they do not have CB1 receptors readily acquire the fearful response, but cannot forget it as easily as do normal mice. These mutant mice continue to respond fearfully to the tone alone, even though it no longer signals that the shock is coming, suggesting that activation of the endocannabinoid system is an essential component of the coping mechanism. Failure to extinguish learned fearful responses may underlie post-traumatic stress syndrome (PTSD) in humans. Stimulation of the endocannabinoid system could be useful in the treatment of PTSD, as it is for treatments of cachexia and spasticity.

Inhalation vs. Digestion

The most direct route of THC administration is by smoking marijuana or other forms of cannabis. Yet purified, FDA-approved medicinal preparations of THC are available in pill form (dronabinol, pure THC marketed as Marinol®, and the analog nabilone, sold as Cesamet® in Canada). If THC is the active agent in cannabis, and approved, orally-effective THC medications exist, why the impetus for medical marijuana? In addition to avoiding all of the legal, political, and social hassles (pot purveyors occasionally being unsavory characters), avoiding inhalation of particulates in smoke is highly desirable on its own. Why not just take a pill?

There are several reasons that some patients prefer puffing over swallowing. One quantitatively minor factor is potential lethality. It is possible to get a fatal overdose by swallowing too many THC pills at once, whereas documented evidence of death simply from smoking too much cannabis does not seem to exist.

More common factors are speed and predictability of action, and degree of patient control. Pills must enter the digestive system, where the rate of entry of THC into the bloodstream is slow and dependent on the state of gastric filling. It can take more than an hour for the full influence of ingested THC to be exerted on the brain, and even that time will vary depending on the timing and
contents of one’s last meal. In contrast, it takes only 20 to 30 seconds for inhaled THC to reach the brain from the lungs and its peak effects are achieved within a few minutes. For someone suffering nausea (itself a significant impediment to the swallowing of medicine or anything else) or chronic pain, the choice is often not a difficult one.

The third factor, controllability, is another serious concern. Once a pill is swallowed, the full dose is on its way with its time-course and side effects to be played out inexorably, governed by the rates of absorption and clearance of the drug from the body. An effective dose that has tolerable side effects in a robust middle-aged man may be too much and have intolerable psychotropic side effects in a slight, elderly woman seeking appetite stimulation to counter the weight loss associated with cancer chemotherapy. With inhalation, patients become adept at sensing and adjusting their intake of THC via smoking (just as people become good at titrating their blood levels of nicotine when smoking tobacco). Because smoked THC enters the brain so quickly, patients can readily detect its presence and adjust their dosing to the level that they need by inhaling less or more. A significant downside to inhalation is that the by-products of burning plant material, particulate and chemical, are taken in and can irritate the mucous membranes of the mouth and lungs. Even though most marijuana smokers do not smoke as much as a pack-a-day tobacco smoker does, bronchitis and the buildup of carcinogenic tars in the lungs do occur in heavy users. Studies of the occurrence of chronic obstructive pulmonary disease, COPD, from cannabis smoking are inconsistent, though. Finally, while generally anxiety-relieving (anxiolytic) in low doses, THC can provoke anxiety and paranoia in high doses, responses that seem exacerbated with inhalation, probably because it acts so quickly.

Some of the drawbacks of smoking cannabis may be circumvented by the use of vaporizers somewhat similar to “e-cigarettes” (electronic cigarettes) that use heating elements to vaporize a liquid nicotine solution. Cannabis vaporizers heat the plant material so that volatile compounds, such as THC, are given off before actual burning and the associated release of particulates, toxins, and carcinogens occurs. Such devices deliver about as much THC as is found in smoke, and are often better tolerated than smoking, although irritation of the mouth and throat are occasional problems. Like e-cigarettes, the designs, efficacy, safety, regulation, and legality of these devices are in flux, but they do provide a potential option for cannabis users who prefer inhalation.
Variation (polymorphisms) among people in the genes encoding CB1 receptors and other endocannabinoid system components affect their cannabinoid drug sensitivity,\textsuperscript{14,15} as well as their susceptibility to disorders related to disturbances of the endocannabinoid system. Links between CB1 polymorphisms and schizophrenia, autism-spectrum disorders, and PTSD have been suggested but remain controversial. Sorting these relationships out is an important task, since the information gained will contribute to the future ideal of personalized medicine.

**Would Having an Entourage Help?**

A final reason for the popularity of smoking over the purified oral THC preparations is subtle and not well understood. For many people, pure THC in pill form is aversive; the unpleasant sensations, “dysphoria,” cause patients not to take their pills. Smoking cannabis is less offensive for some of these patients, suggesting that something besides THC is involved. THC is the only psychotropic cannabinoid, but one or more of the non-psychotropic cannabinoids could modulate or soften the impact of pure THC in several ways: they might act as part of an “entourage,”\textsuperscript{16} unable to activate CB1 themselves, but capable of modifying THC’s ability to do so. Alternatively, non-psychotropic cannabinoids might influence other components of the endocannabinoid system (synthesis, uptake, or degradation), and thus alter availability of endocannabinoids, which compete with THC for access to CB1, and thereby indirectly tweak THC’s actions.\textsuperscript{17} But interactions with the endocannabinoid system are not the only possibilities. Non-psychotropic cannabinoids can affect conventional neurotransmitter receptors and ion channels that are entirely unrelated to the endocannabinoid system.\textsuperscript{18} (They are “cannabinoids” because they come from the cannabis plant, not because they necessarily have anything to do with CB1, CB2, or the ECS in general.)

Cannabidiol (CBD) is a major non-psychotropic cannabinoid, and is almost as abundant as THC. Interestingly, while the CBD:THC ratio varies in different strains of cannabis, the total amount of cannabidiol plus THC across strains is roughly constant. The more THC, the less cannabidiol, and vice versa. The proportion of CBD:THC is selected for in cannabis plant-breeding programs. Cannabidiol can inhibit CB1 (and CB2) directly, and this may diminish THC’s CB1-mediated undesirable actions,\textsuperscript{17} which are dose-related. For example, cannabidiol blunts the anxiogenic and psychotropic side effects of THC. In addition to synergistic actions, cannabidiol by itself is anxiolytic,\textsuperscript{18} and can reduce inflammation and blood pressure.\textsuperscript{19} A mucosal spray, Sativex\textsuperscript{®} (GW Pharmaceuticals), a botanical
extract of cannabis plants, has a standard CBD:THC ratio of 1. In Canada, the United Kingdom, and other countries (not yet the United States), Sativex® is available for the treatment of the pain and spasticity of multiple sclerosis.

The anticonvulsant properties of cannabis have been known for centuries. A dramatic account of such action recently received widespread media coverage. A young child suffering from an intractable form of childhood epilepsy called Dravet syndrome had been unsuccessfully treated with a battery of epilepsy therapies for years since her first seizure at three months of age. By age five, she was having up to 300 seizures per day, and experiencing mental and physical developmental stagnation. Her prospects were grim and her parents desperate. With the approval of two doctors, they tried adding an oil extract of cannabis to her food. Amazingly, her seizures immediately dropped to a few per month, an improvement that has persisted for a year, and her normal development resumed.

A notable feature of this case, which has been repeated in other similarly afflicted children, is that her cannabis extract is from a strain (called “Charlotte’s Web”) that is very low in THC and high in cannabidiol. To what extent this positive outcome is attributable to the low THC, the high cannabidiol, or the combination of the two is unknown. A different non-psychotropic cannabinoid, cannabidivarin, reduces seizures independently of CB1 in animal models, and this property is not improved by the presence of THC.

**Turning On (or Off)**

CB1 receptors exist on nerve fibers outside of the central nervous system, and there they also direct communications traffic. Psychotropic side effects of cannabis are caused exclusively by turning on or off brain CB1s. Therefore one strategy is to develop CB1 agonists or antagonists that can be given orally but that do not cross the blood-brain barrier (a membranous cellular fence that bars certain chemicals present in the circulation from getting into the brain). CB1s in fat and other tissues are thought to contribute to obesity, and a peripherally restricted CB1 antagonist could be beneficial in weight control. Conversely, cannabinoids are good pain relievers that work in part by stimulating CB1s on peripheral pain sensory neurons. When activated, these CB1s block transmission of the pain signals to the brain—basically what topical anesthetics like novocaine do—and pain signals
unable to reach the brain are not felt. CB1 agonists or antagonists that are restricted from the brain could be quite useful in conditions that do not arise from within the central nervous system.

What about manipulating other components of the endocannabinoid system? Rather than stimulating CB1 with drugs, the endocannabinoids can be pressed into service artificially. Once released, endocannabinoids, like other chemical messengers, are quickly taken back up into cells or otherwise inactivated, which preserves the integrity of the signaling process. Inhibiting uptake and degradation therapeutically offers the advantage of increasing the endocannabinoid levels, and thereby activating CB1, in those regions in which the messengers are already being mobilized by brain activity itself. Rather than indiscriminate activation of CB1s everywhere for long periods of time, only certain groups of receptors would be activated and only when and where called for naturally. With a drug that inhibits the enzyme (fatty-acid amide hyrolase, FAAH) that inactivates the endocannabinoid, anandamide (but not 2-AG), levels increase, and an analogous approach inhibits the major degradation enzyme for 2-AG, monoglyceride lipase (MGL) and 2-AG levels rise. Elevations in endocannabinoids in this way can have beneficial effects. Unfortunately, there are still problems: in addition to activating CB1, anandamide turns out to be an excellent activator of a non-cannabinoid receptor, TRPV1, a non-cannabinoid receptor that actually heightens anxiety, so globally elevating anandamide has complex effects. Drugs that inhibit both FAAH and TRPV1 could be helpful in some cases. Meanwhile, globally elevating 2-AG by decreasing its breakdown overloads the endocannabinoid system, which responds by causing a protective shutdown, or down regulation, of many CB1s in the brain. This is counterproductive if the goal is stimulation of the endocannabinoid system.

An encouraging development along these lines is that the peripheral pain signals can be quashed by raising anandamide and 2-AG levels only near the site of origin (a rat’s paw), where a painful stimulus was given. This means that the local peripheral CB1 and CB2 receptors in the paw were effectively turned on by the elevation in endocannabinoid levels resulting from prevention of their breakdown. In this case, pain relief free of psychotropic side effects should be possible with degradative enzyme blockers designed to stay out of the central nervous system.

Finally, a possibility that has gotten little attention is the targeting of conventional neurotransmitter systems that stimulate the production of endocannabinoids. For example, glutamate is the major
excitatory neurotransmitter in the brain, and one subtype of glutamate receptors (group I mGluRs) potently mobilizes endocannabinoids.\textsuperscript{29,30} A genetic disease that causes mental retardation, fragile X syndrome, has long been associated with excessive activity at the same glutamate receptors,\textsuperscript{31} which could be related to the excess production of endocannabinoids at inhibitory synapses in a mouse model of the disease.\textsuperscript{32} Perhaps combining modest inhibition of both CB1 and group I mGluRs would be a way of tapping the therapeutic potential of the ECS, while avoiding some of its problems.

**What Is in Store?**

The endocannabinoid system is powerful and nearly ubiquitous in the nervous system. The cannabinoid receptors dispersed throughout many brain regions are responsible for regulation of numerous aspects of neuronal activity, and account for the bewildering variety of behavioral and psychological effects caused by THC. Depending on the nervous system regions and maladies involved, either stimulating or inhibiting the endocannabinoid system could have beneficial effects. A great deal of attention is being given to incorporating non-psychotropic cannabinoids into medicinal preparations, although in most cases the actual effects of these agents on the nervous system are unknown. For some purposes, drugs that are restricted to acting on peripheral cannabinoid receptors, and are prevented from entering the central nervous system, could be effective. Finally, therapeutic strategies aimed at developing regionally selective targeting of endocannabinoid system components, perhaps in combination with agents that affect conventional neurotransmitter systems, or non-psychotropic cannabinoids, offer promise for future advances.

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retrograde signaling in the brain. DSI was eventually found to be mediated by endocannabinoids by the laboratories of R. Nicoll and M. Kano, and is the first instance of a physiological process carried out by endocannabinoids. In all, Alger’s group has published over 100 research papers on the regulation of inhibition, focusing mainly on DSI and endocannabinoids in the past two decades.

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