

The Discovery of the Endocannabinoid System

The National Institute on Drug Abuse inadvertently facilitated a series of major discoveries about the workings of the human brain.

By Martin A. Lee

Up until the late 1980s, Cannabis research remained a rather esoteric field involving a small number of scientists in the United States and abroad. Their efforts were circumscribed by the politicized agenda of the National Institute of Drug Abuse, which subsidized studies designed to prove the deleterious effects of cannabis while blocking inquiry into its potential benefits.

Rather than discrediting cannabis, NIDA inadvertently facilitated a series of major discoveries about the workings of the human brain. These breakthroughs — among the most exciting developments in brain chemistry of our time — spawned a revolution in medical science and a profound understanding of health and healing.

“By using a plant that has been around for thousands of years, we discovered a new physiological system of immense importance,” says Raphael Mechoulam, the dean of the transnational cannabinoid research community. “We wouldn’t have been able to get there if we had not looked at the plant.”

In the two decades following the identification and synthesis of THC by Mechoulam and his colleague Y. Gaoni in Israel in 1964, scientists learned a great deal about the pharmacology, biochemistry and clinical effects of cannabis. But no one really knew how it worked — what it actually did inside the brain on a molecular level to alter consciousness, stimulate appetite, dampen nausea, quell seizures, and relieve pain. No one understood how smoked marijuana could stop an asthma attack in seconds, not minutes. No one knew why it lifted one’s mood.

When American researchers at Johns Hopkins University identified receptor sites in the brain capable of binding with opioids (such as morphine and heroin) in 1973, some scientists expected that the discovery of receptor sites for marijuana would soon follow. But 15 years would elapse before a U.S.-government-funded study at the St. Louis University School of Medicine determined that the mammalian brain has receptor sites — specialized protein molecules embedded in cell membranes — that respond pharmacologically to compounds in marijuana resin.

Initially identified by Allyn Howlett and William Devane, cannabinoid receptors turned out to be far more abundant in the brain than any other type of neurotransmitter receptor.

A potent THC analog synthesized by Pfizer (CP55,940) enabled researchers to radioactively tag and begin mapping the precise locations of cannabinoid recep-

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tors in the brain. Not surprisingly, they are concentrated in regions responsible for mental and physiological processes: the hippocampus (memory), cerebral cortex (higher cognition), the cerebellum (motor coordination), the basal ganglia (movement), the hypothalamus (appetite), the amygdala (emotions) and elsewhere.

On July 18, 1990, at a meeting of the National Academy of Science’s Institute of Medicine, Lisa Matsuda announced that she and her colleagues at the National Institute of Mental Health (NIMH) had achieved a major breakthrough — they had pinpointed the exact DNA sequence that encodes a THC-sensitive receptor in the rat’s brain.

Cannabinoid receptors function as subtle sensing devices, tiny vibrating scanners perpetually primed to pick up biochemical cues that flow through fluids surrounding each cell.

People have the same receptor, which consists of 472 amino acids strung together in a crumpled chain that squiggles back and forth across the cell membrane seven times. Cannabinoid receptors function as subtle sensing devices, tiny vibrating scanners perpetually primed to pick up biochemical cues that flow through fluids surrounding each cell.

Matsuda also disclosed that she had successfully cloned the marijuana receptor. This electrifying news was the curtain-raiser for “the Decade of the Brain,” as it was proclaimed at the National Academy of Science meeting. During the 1990s, there would be more advances in neuroscience than in all previous years combined.

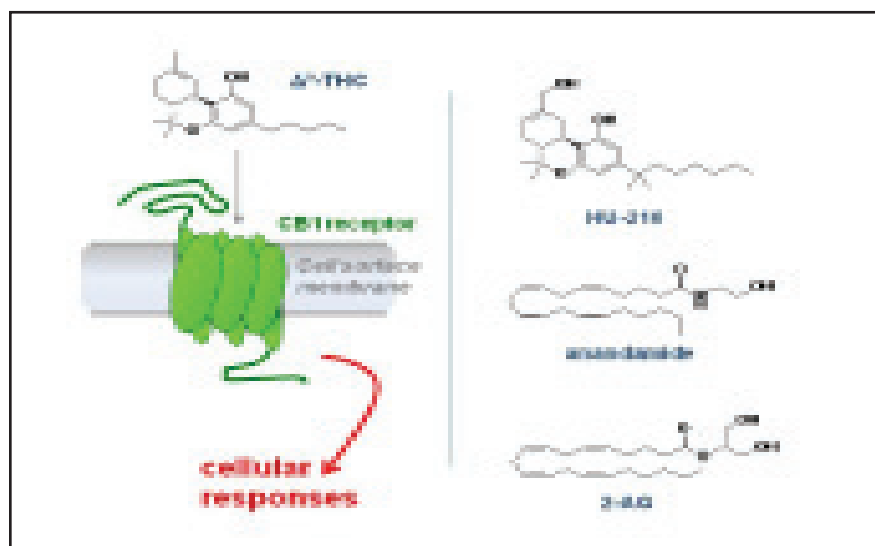
The cloning of the cannabis receptor was crucial. It opened the door for scientists to sculpt molecules that “fit” these receptors like keys in a slot. Some keys — “agonists” — turned the receptor on, others — “antagonists” — turned it off.

Scientists also developed genetically engineered “knockout” mice that lacked this receptor. When administered to knockout mice, THC had virtually no effect; the THC had nowhere to bind and hence could not trigger any activity. This was further proof that THC works by activating cannabinoid receptors in the brain and central nervous system. Finally, after 50 centuries of medicinal usage, the scientific basis of cannabis therapeutics was coming into focus.

Researchers soon identified a second type of cannabinoid receptor, dubbed “CB2,” which is prevalent throughout the immune system and the peripheral nervous system. CB2 receptors are also present in the gut, spleen, liver, heart, kidneys, bones, blood vessels, lymph cells, endocrine glands and reproductive organs.

The CB1 receptor mediates psychoactivity. CB2 regulates immune response. Marijuana does so much and is such a versatile medicine because it acts everywhere, not just in the brain.

Just as the study of opium resulted in the discovery of endorphins, the brain’s



CANNABINOIDS ACT BY BINDING TO RECEPTOR PROTEINS spanning the membranous surface of cells and encoded by either the CB1 or CB2 receptor genes. Activation of the CB receptors changes cellular function, including gene expression and electrical excitability of cell membranes, by triggering intricate cascades of intracellular signaling molecules. The chemical structure of delta 9-THC, the classic and prototypical cannabinoid of the cannabis plant, has been modified to create synthetic analog drugs like HU-210, which is many times more potent an agonist (chemical activator) of the CB1 receptor.

Such potent drugs have been very useful experimentally because they drive the receptor more intensely than do THC or the endocannabinoids. While this property (being a “high-efficacy full agonist”) can create more readily observable results when compared to a partial agonist like THC, such experiments are frequently and inaccurately publicized as revealing a specific effect of marijuana. Anandamide and 2-AG are CB receptor agonists that evolved in the natural world many millions of years before the cannabis plant itself, and are innate chemical regulators within possibly every animal and in most tissues of the human body (even in insects that lack the CB receptors, 2-AG is present and acts at different targets). The chemical structures of the endocannabinoids are quite different from the phytocannabinoids, although there is evidence that they may fold in a way that resembles THC in 3-D space.

own morphine-like substance, so, too, marijuana research would lead to the discovery of a natural, internal, THC-like compound, our “inner cannabis,” so to speak. In 1992, Raphael Mechoulam, in collaboration with NIMH research fellow William Devane and Dr. Lumir Hanus, found a novel neurotransmitter, a naturally-occurring “endocannabinoid,” which attaches to the same mammalian brain-cell receptors as THC. They decided to call it “anandamide,” deriving from the Sanskrit word for bliss.⁶

In 1995, Mechoulam’s group discovered a second major endocannabinoid — 2-arachidonoylglycerol, or “2-AG” — that “locks on” to both the CB1 and CB2 receptors.

By tracing the metabolic pathways of THC, scientists stumbled upon a unique and hitherto unknown molecular signaling system that is involved in regulating a broad range of biological functions. Scientists call it “the endocannabinoid system,” after the plant that led to its detection. The name suggests that the plant came first, but in fact, as Dr. John McPartland has explained, this ancient, internal signal system started evolving over 600 million years ago (long before cannabis appeared) when the most complex life form was sponges.¹

Endocannabinoids and their receptors are present in fish, reptiles, earthworms, leeches, amphibians, birds and mammals — every animal except insects. Given its long evolutionary history, scientists surmised that the endocannabinoid system must serve an important and basic function in animal physiology.

The effects of cannabis have drawn scientists to the still unfolding saga of the endocannabinoid system, which has only recently begun to reveal its profound mysteries. Endocannabinoids and their receptors emerged as a hot topic among scientists who shared their findings in highly technical peer-reviewed journals and at annual conclaves hosted by the

International Cannabinoid Research Society (ICRS). Formed in 1992, the society and many of its members (mainly university-connected scientists) were supported by U.S government research grants.

ICRS proceedings piqued the interest of big pharmaceutical firms. Drug company investigators paid close attention to cutting-edge developments in cannabinoid science, which few people outside the scientific community were privy to. Advances in the burgeoning field of cannabinoid studies would pave the way for new treatment strategies for various pathological conditions — cancer, diabetes, neuropathic pain, arthritis, osteoporosis, obesity, Alzheimer’s, multiple sclerosis, depression and many other diseases that seemed beyond the reach of conventional cures.

CB1 and CB2 receptors recognize and respond to three kinds of cannabinoid agonists (turn-on keys): endogenous-fatty-acid cannabinoids; phyto-cannabinoids concentrated in the oily resin on the buds and leaves of the marijuana plant; and synthetic cannabinoids concocted in university and drug company laboratories.

For Big Pharma, cannabinoid research became a tale of knockout mice and men. Using genetically-engineered rodents that lacked CB receptors, researchers were able to prove that cannabinoid compounds can alter disease progression and attenuate experimentally-induced symptoms.

An “animal model” of osteoporosis, for example, was created in normal mice and in knockout mice lacking CB receptors. When a synthetic cannabinoid drug was given to both groups of osteoporotic mice, bone damage was mitigated in the normal mice but had no effect on rodents sans CB receptors — which means that CB receptors are instrumental in regulating bone density.

continued on next page

The Endocannabinoid System *from previous page*

A German research team would later prove that CB2 receptor activation restrains the formation of bone reabsorbing cells, known as osteoclasts, by down-regulating osteoclast precursors, thus tipping the balance in favor of osteoblasts, cells that facilitate bone formation.

Other experiments would establish that CB-receptor signaling modulates pain and analgesia, inflammation, appetite, gastro-intestinal motility, and sleep cycles, along with the ebb and flow of immune cells, hormones, and other mood-altering neurotransmitters such as serotonin, dopamine, and glutamate.

Glucose metabolism in every cell of the human body is regulated by the endo-cannabinoid system. Formed “on demand” from fatty acid precursors in areas of need, anandamide and 2-AG impact the organism in ways that are “predominantly local and specific,” says Mechoulam. “Their actions are ubiquitous. They are involved in most physiological systems that have been investigated.”²

Retrograde signaling serves as an inhibitory feedback mechanism that tells other neurotransmitters to cool it when they are firing too fast.

When tickled by THC or its endogenous cousins, cannabinoid receptors trigger a cascade of biochemical changes on a cellular level that puts the brakes on excessive physiological activity. Endocannabinoids are the only neurotransmitters that engage in “retrograde signaling,” a form of intracellular communication that inhibits immune response, reduces inflammation, relaxes musculature, lowers blood pressure, dilates bronchial passages, and normalizes overstimulated nerves. Retrograde signaling serves as an inhibitory feedback mechanism that tells other neurotransmitters to cool it when they are firing too fast. (See illustration at right.)

“Endocannabinoids are central players in life’s multidimensional biochemical balancing act known as homeostasis,” says biologist Robert Melamede, who describes the endocannabinoid system as “the Ur-Regulator,” the master modulator, which is constantly multitasking, adjusting and readjusting the complex network of molecular thermostats that control our physiological tempo.

The human immune system, an amazing physiological wonder, kicks on like a furnace when a fever is required to fry a virus or bacterial invader. And when the job is done, endocannabinoid signaling turns down the flame, cools the fever, and restores homeostasis. (Cannabinoids —endo, herbal, and synthetic— are anti-inflammatory; they literally cool the body.)

But if the feedback loop is out of control, if the pilot light burns too high, if the immune system overreacts to chronic stress or mistakes one’s body for a foreign object, then the stage is set for an autoimmune disease or an inflammatory disorder to develop.

Prior to the discovery of the endocannabinoid system, retrograde signaling was known to occur only during the embryonic development of the brain and nervous system.³ Endocannabinoids choreograph “a broad array of developmental processes in the embryonic brain,” as McPartland put it, including neural stem cell proliferation and differentiation, a process guided by extracellular cues conveyed via CB receptors.⁴

By the time the Decade of the Brain had run its course, scientists would learn that CB receptor signaling also regulates adult neurogenesis (brain cell growth) and stem cell migration.

High endocannabinoid levels in the brain are triggered by strokes and other neurological insults —attesting to the neuroprotective properties of the endo-cannabinoid system, which can be viewed as part of the body’s “general protective network, working in conjunction with the immune system and various other physiological systems,” according to Mechoulam.⁵ His Nobel-worthy discoveries posed a direct challenge to scientific orthodoxy by revealing that the brain has a natural repair kit, an in-built mechanism of protection and regeneration, which can mend damaged nerves and brain cells.

The discovery of the endocannabinoid system has breathtaking implications for nearly every area of medicine, including reproductive biology. Dr. Mauro Maccarrone at the University of Teramo, Italy, describes the endocannabinoid system as the “guardian angel” or “gatekeeper” of mammalian reproduction.

Endocannabinoid signaling figures decisively throughout the reproductive process —from spermatogenesis to fertilization, oviductal transport of the zygote, embryo implantation, and fetal development. CB receptors proliferate in the placenta and facilitate neurochemical “cross-talk” between the embryo and the mother.

A misfiring of the endocannabinoid system could result in serious problems, including ectopic pregnancy and miscarriage. (A deficiency of anandamide, the bliss molecule, can cause spontaneous abortions in mammals.) High levels of endocannabinoids in maternal milk are critically important for the initiation of suckling in newborns. Infant colic has been attributed to a dearth of endocannabinoids.

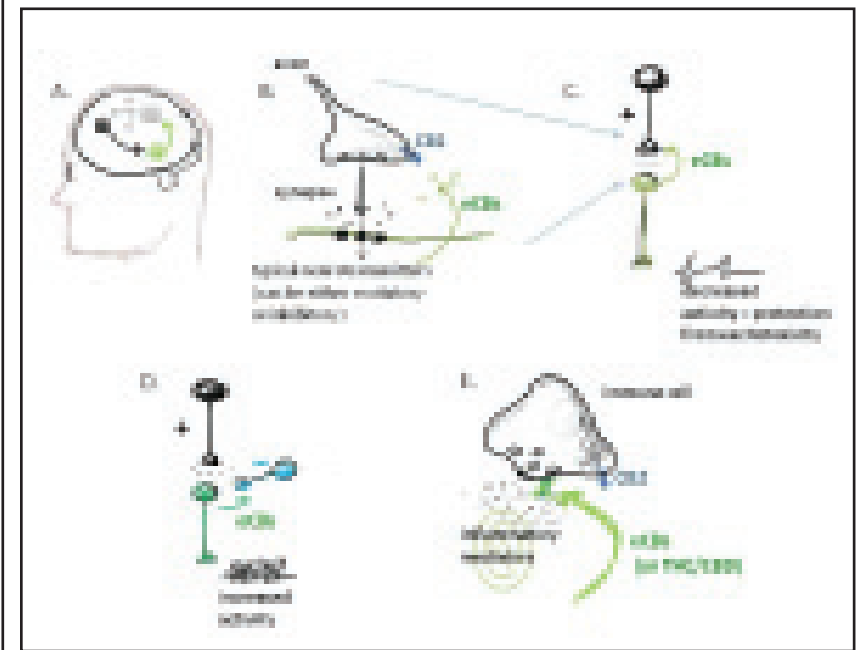
Israeli neuroscientist Ester Fride observed that knockout mice missing CB receptors resemble babies who suffer from “failure to thrive” syndrome. (Without CB receptors, mice wither and die prematurely.) This is one of many enigmatic conditions that may arise because of a dysfunctional endocannabinoid system.

Endogenous cannabinoid deficiency could result from too few cannabinoid receptors or the insufficient presence of anandamide and/or 2-AG. Individuals have different congenital endocannabinoid levels and sensitivities.

Whether the result of poor diet, lack of exercise, drug abuse, environmental toxins or genetic factors, endocannabinoid deficits are associated with a reduced ability or inability to adapt to chronic stress. Prolonged exposure to stress depletes endocannabinoid tone, and this, in turn, has an adverse impact on a plethora of physiological processes. University of Washington neurologist Ethan Russo postulates that “clinical endocannabinoid deficiency” underlies migraines, fibromyalgia, irritable bowel disease, and a cluster of other degenerative conditions, which may respond favorably to cannabinoid therapies.⁶

Ironically, the U.S. government’s unending search for marijuana’s harmful properties yielded astonishing scientific insights that validate the herb’s therapeutic utility. By stimulating CB1 and CB2 receptor signaling, marijuana functions as a substitute “retrograde messenger” that mimics the way our bodies try to

How Endocannabinoids Work (negative feedback)



ENDOCANNABINOIDS are short-lived signaling molecules that function as retrograde synaptic messengers at synapses of the brain.

A) Imagine three different areas of the brain: one communicates to the next through many neurons (brain cells), which send long processes (axons) to form connections (synapses) with the surface of target cells in the next brain area.

B) At synapses, conventional neurotransmitters are released from the ends of axons and bind to receptors on target cells, causing either an excitation or inhibition of that cell within its brain circuit. The endocannabinoids work in reverse, and bind to CB1 receptors on axon terminals, turning down the level of neurotransmitter release. The outcome of this signal —that is, the effect the cannabinoid receptor has on brain activities and higher order functions like emotion and memory— is very complex, and is inspiring new ideas of how the brain processes information and maintains internal balance, or homeostasis.

C) For example, when cannabinoids inhibit release from excitatory neurons (indicated by the + sign), the net result is a decreased activity of the target cell and its protection from excitotoxicity: a word that describes the deadly over-excitation of neurons in many pathological conditions such as stroke and epilepsy. This is a key finding, demonstrated by numerous labs looking in many brain areas, and reveals the endocannabinoids as an innate defense mechanism of the brain. It also helps explain how cannabinoids could help lessen the damaging effects of stroke, epilepsy and perhaps other brain traumas.

D) When endocannabinoids target certain strategically located inhibitory neurons (-), the net result is an increased activity in target cells. This can have complex effects, such as altering synchrony with other neurons in the network. Such a transient regulation of neuronal firing frequency by endocannabinoids is likely to be important for many brain activities, ranging from the regulation of body temperature and stress, to the perception of pain, fear, space and time.

E) Although CB2 receptors reside mostly on immune cells rather than neurons, activation by cannabinoids leads to related cellular outcomes. Release of inflammatory mediators is decreased and cell migration is inhibited, which can dampen the painful and sometimes destructive symptoms of an immune response. This is a simplified description of what has become a strong scientific rationale to investigate cannabinoids as therapies for autoimmune diseases, stroke, and a number of serious neurodegenerative diseases (which often involve years of chronic brain inflammation).

—Gregory Gerdeman

maintain balance. Cannabis is a unique, natural medicine that taps into how we work biologically on a very deep level. Thanks to this plant, scientists have been able to decipher the primordial language that nerves and brain cells use to communicate. From womb to tomb, across countless generations, the endocannabinoid system guides and protects.

But a big disconnect existed between the world of science and the general

public during the Decade of the Brain. Aside from certain segments of the scientific community, few people knew about the endocannabinoid system. Doctors, journalists, public officials —hardly anyone was clued into the latest scientific research that went a long way toward explaining why marijuana is such a versatile remedy and why it is, by far, the world’s most popular illicit substance.

References

- 1 McPartland, M, Guy G. “The evolution of Cannabis and coevolution with the cannabinoid receptor - a hypothesis,” in Guy, et al, eds., *The Medicinal Uses of Cannabinoids*; and McPartland JM et al. “Evolutionary origins of the endocannabinoid system,” *Gene*. 2006;370:64-74.
- 2 “Conversation with Raphael Mechoulam,” *Addiction*, 102:887-893 (2007).
- 3 Roger A. Nicoll and Bradley E. Alger, “The Brain’s Own Marijuana,” *Scientific American*, December 2004.
- 4 John M. McPartland, “The Endocannabinoid System: An Osteopathic Perspective,” *JOAO*, October 2008.
- 5 C. Pope, R. Mechoulam, L. Parsons, “Endocannabinoid Signaling in Neurotoxicity and Neuroprotection,” in *Neurotoxicology*, Dec. 4, 2009.
- 6 Ethan B. Russo, “Clinical Endocannabinoid Deficiency,” *Neuroendocrinology Letters* Nos. , Feb-Apr Vol. 25, 2004