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 scientists and organizations designed to prove the deleterious effects of cannabis while blocking inquiry into its potential benefits.

Rather than discounting cannabis, NIDA inadvertently facilitated a series of major discoveries about the workings of the human brain. These breakthroughs—a long among the developments in brain chemistry of our time—spun 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, biochemical and clinical effects of cannabis. But no one really knew how it worked—what it actually did inside the brain. Novel insights into how consciousness, stimulant, appetite, dampened sense, quelled seizures, and relieved pain. No one even knew 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 1975, some scientists speculated 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 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 more abundant in the brain than any other type of neurotransmitter receptor. A potent THC analog synthesized by Pfizer (CP55,444) enabled researchers to radioactively tag and begin mapping the precise locations of cannabinoid receptors in the brain. CB2 receptors.

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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; 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. The cloning of the cannabis receptor.

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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. In 1976, Mechoulam identified a cannabinoid receptor function as subtle sensing devices, tiny vibrating scanners percutaneously primed to pick up biochemical cues that flow through fluids surrounding each cell.

Endocannabinoids are vertebrates, amphibians, birds and mammals present in fish, reptiles, earthworms, nematodes, and men. Using genetically-engineered rodents that lacked CB receptors, researchers were able to prove that cannabis binds to specific receptors in the brain.

Endocannabinoids and their receptors are present in fish, reptiles, earthworms, leeches, amphibians, birds and mammals—all animal excreta. 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 been drawn by 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 journal articles and at annual conclaves hosted by the International Cannabis Research Society (ICRS). Formed in 1992, the society and 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 investors 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 prove 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 developed by university and drug company laboratories.

For Big Pharma, cannabinoid research became a race to the finish line.

The Prop 215 Era

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CB1 receptor mediates psychoactivity. CB2 regulates immune response. Marijuana does so much more than lift the spirits. It is a unique medicine because it acts everywhere, not just in the brain.

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The Endocannabinoid System

A German research team would later prove that CB2 receptor activation represses the formation of reabsorbing cells, known as osteoclasts, by down-regulating osteoclast precursors, thus tipping the balance in favor of bone formation, cells that facilitate bone formation. Other experiments would establish that CB receptor signaling modulates pain and analgesia, inflammation, apoptosis, gut-intestinal motility, and sleep cycles, along with the ebb and flow of immune cells, hormones, and other modulators of 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.”

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 endoge- nous cousin, cannabinoi ds, retrograde signaling triggers a cascade of biochemical changes on a cellular level that puts the brakes on excessive physiological activity. Endocan- nabinoids are the only neurotransmitters that engage in “retrograde signaling,” a form of intracellular communication that inhibits immune response, reduces inflammation, relaxes muscle, lowers blood pressure, dilates bronchial passages, and normalizes oscillated 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 biochemi- cal balancing act known as homeostasis,” says biologist Robert Melamede, who describes the endocannabinoid system as “the Ur-Regulator,” the master modula- tor, which is constantly monitoring, 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 — aged or synthetic, 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 for- eign object, then the stage is set for an autoimmune disease or an inflammatory disorder to develop.

Prior to the discovery of the endocan- nabinoid system, retrograde signaling was known to occur only during the embryonic development of the brain and nervous system. Endocannabinoids chro-nicling “a broad array of development- al 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 be astonished to hear 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 conjunc- tion with the immune system and other physiological systems,” according to Mechoulam.5 His Nobel-worthy discoveries posed a direct challenge to the 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 endocanbanoid system has breathtaking implications for nearly every area of medicine including reproductive biology. Dr. Mauro Maccarrone at the University of Teramo, Italy, describes the endocan- nabinoid system as “guardian angel” or “gatekeeper” of mammalian repro- duction. Endocannabinoid signaling figures decisively throughout the reproductive process — from spermatogenesis to pregnancy, ovumual transport of the zygote, embryo implantation, and fetal development. CB receptor proliferate in the placenta and facilitate neurological “cross-talk” between the embryo and the mother. A misfiring of the endocannabinoid system could result in serious problems, including ectopic pregnancy and miscar- ria. Birth defects caused by 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 endocan- nabinoids.

Israeli neuroscientist Esther Fridere observed that knockout mice missing CB receptors experience babies who suf- fer from “failure to thrive” syndrome. (Without CB receptors, mice wither and die prematurely.) This is one of many examples of what might go wrong because of a dysfunctional endocan- nabinoid 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 endocan- nabinoid levels and sensitivities.

Whether the result of poor diet, lack of exercise, drug abuse, environmental toxins or genetic factors, endocannabi- nor 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 host of other de- generative conditions, which may respond favorably to cannabinoid therapies.6

Ironically, the U.S. government’s unrelenting 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 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 primal language that nerves and brain cells use to com- municate. From womb to tomb, across countless generations, the endocan- nabinoid system guides and protects.

But a big discussion on the existence of this 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. Doc- tors, journalists, public officials — hardly anyone was consulted in the latest scientific research that went a long way toward explaining why marijuana is such a ver- satile remedy and why it is, by far, the world’s most popular illicit substance.

References