Introducing a special section from Smoke Signals, the new “social history of marijuana” by Martin A. Lee

The Riddle of THC

On August 28, 1964, the day Bob Dylan lit up and handed the Beatles their first joint in a New York City hotel room, Dr. Raphael Mechoulam was working intensively in his laboratory at the Hebrew University in Jerusalem. The young Israeli chemist and his research partner, Yechiel Gaoni, would soon become the first scientists to fully isolate and synthesize delta-9-tetrahydrocannabinol, or THC, marijuana’s principal psychoactive component.

Mechoulam’s ground-breaking research was subsidized by the U.S. National Institutes for Health (NIH), which had suddenly become desirous of more objective information about the herb. In the mid-1960s, NIH had convened a panel of experts to study marijuana. The panel’s report, published in 1969, recommended that marijuana research be accelerated to help resolve “a variety of perplexing problems,” including whether cannabis could be used to cure brain damage and addiction. But the panel withheld its report from Congress, saying it would be premature to make a decision about marijuana before more research was done. In fact, it would be more than two decades before Congress would consider any legislation on marijuana.

As the use of marijuana skyrocketed among middle class youth, officials began to get anxious, especially when the sons and daughters of prominent politicians were caught smoking it. Queried by members of Congress as to whether pot caused brain damage, the NIH seemed to gather basic scientific data. But bombast was the order of the day. Convulsions, scurvy, fits of rage, and violence were just a few of the side effects predicted with marijuana. By the late 1960s, eleven states had banned marijuana. While the cause of action was marijuana’s psychoactive effects, the real cause lay in the effects of a second compound, the cannabinoid—known as “cannabinoids”—that were unique to the marijuana plant. In addition to tetrahydrocannabinol (THC), marijuana contains various alkaloids, flavonoids, and terpenoids (essential aromatic oils).

The isolation and synthesis of THC would prove to be a highly significant event in the history of psychopharmacology. Mechoulam, then 34, announced his discovery in a letter to the editor of the Journal of the American Chemical Society on July 20, 1965. Although he didn’t realize it at the time, Mechoulam had lit a slow-burning fuse that would detonate a revolution in medical science.

The Brain and Marijuana

When American researchers at Johns Hopkins University identified receptor sites in the brain capable of binding with opiates in 1973, some scientists expected that the discovery of a receptor for marijuana might soon follow. But these were difficult to pin down. Fifteen years would elapse before a 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 cannabinoids. Scientists would eventually ascertain that at least 100 of these lipophilic compounds — known as “cannabinoids” — are unique to the marijuana plant. In addition to the cannabinoid, a term coined by Mechoulam, marijuana contains various alkaloids, flavonoids, and terpenoids (essential aromatic oils).

Some keys (“agonists”) turned the receptor on; others (“antagonists”) turned it off. In addition to synthesizing cannabinoid receptor agonists and antagonists, scientists experimented with genetically engineered “knockout” mice that lacked this receptor. When administered to knockout mice, cannabinoid agonists mimicked natural pain-killing effects. THC stimulated the CB-2 receptors (which are not concentrated in the brain); THC binding to CB-1, the central nervous system receptor, causes the high. The CB-1 receptor mediates psychoactivity. CB-2 regulates immune response. Marijuana is such a versatile substance because it acts everywhere, not just in the brain.

Just as the study of opium resulted in the discovery of endorphins, the brain’s own morphinelike substance, so, too, marijuana research would lead to the discovery of a natural, internal THC-like compound, our “inner cannabinoids,” 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 endogenous (meaning “made internally”) cannabinoid. This “endocannabinoid” attaches to the same mammalian brain cell receptors as THC. Mechoulam decided to call it “anandamide,” deriving from the Sanskrit word for bliss. In 1995, his group discovered a second major endocannabinoid molecule, 2-AG (2-arachidonoylglycerol), which binds to both CB1 and CB-2 receptors.

By tracing the metabolic pathways of THC, scientists had stumbled upon a hitherto unknown molecular signaling system that plays a crucial role in regulating a broad range of biological processes. This molecular signaling system modulates how we experience pain, stress, hunger, sleep, our circadian rhythms, our blood pressure, body temperature, bone density, fertility, intestinal fortitude, mood, metabolism, memory retention, and more.

Scientists call it “the endocannabinoid system” — so named after the plant that led to its discovery. The name suggests that the plant came first, but in fact, as Dr. John McPartland explained, this ancient internal signal system started evolving more than 500 million years ago (long before cannabis appeared), when the most complex life-forms, the sponges. Endocannabinoids and their receptors are present in fish, reptiles, earthworms, leeches, amphibians, birds, and mammals — every animal except insects. Its long evolution history indicates that the endocannabinoid system must serve a very important and basic purpose in animal physiology.

Drug-company investigators paid close attention to cutting-edge developments in cannabinoid research, which few people outside the scientific community were privy to. Endocannabinoids and their receptors emerged as a hot topic among scientists who shared an interest in pain research and pharmaceuticals. In 1983, Dr. Raphael Mechoulam and his colleagues at the Hebrew University and the University of California, San Francisco, published a landmark paper on the endocannabinoid system in the journal Nature. In 1988, the International Cannabinoid Research Society (ICRS) was formed as a professional organization for scientists interested in the endocannabinoid system. By 1994, the ICRS had 310 members worldwide.

In 1992, Mechoulam and his colleagues — including Israeli scientist Ester Fride — observed that knockout mice missing CB receptors resemble newborns. Infant colic has been attributed to a dearth of endocannabinoids. In addition, scientists found that endocannabinoids are synthesized in the placenta and brain during the prenatal period. Appropriate levels of endocannabinoids in the placenta and brain during pregnancy seem to protect a developing fetus against brain damage. Fride observed that knockout mice missing CB receptors resemble babies who suffer from “failure to thrive” syndrome.

Pathological conditions involving dysregulation of endocannabinoid-cb2 signaling may respond favorably to pharmacological interventions. For Big Pharma, cannabinoid receptors are promising targets for the development of new therapeutic agents. By combining cannabinoid agonists and antagonists, scientists can develop drugs that have both beneficial and therapeutic effects. For example, cannabidiol, a non-psychoactive compound found in cannabis, has been shown to have anti-inflammatory and anti-anxiety properties. By understanding the endocannabinoid system and its role in the brain, scientists can develop new treatments for a variety of medical conditions. However, the development of cannabinoid-based therapies is complicated by the fact that cannabis is a Schedule I drug, which means that it has a high potential for abuse and lacks any currently accepted medical use.

Israel's medical cannabis market has been growing rapidly, with government approval for the use of medicinal cannabis for a variety of conditions, including chronic pain, multiple sclerosis, epilepsy, and glaucoma. However, the use of medicinal cannabis remains controversial, with some politicians and medical professionals advocating for greater legalization and research, while others are concerned about the potential for abuse and the lack of regulation. As the research on the endocannabinoid system continues to advance, it is likely that new treatments will be developed to help alleviate symptoms associated with a variety of medical conditions. However, the development of these treatments will require further research and collaboration between scientists, regulatory agencies, and policymakers.
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 without cannabinoid receptors. Surprisingly, cannabinoid tissue was given to both groups of osteoporotic mice. A bone damage was mitigated in the normal mice but had no effect on rodents sans CB receptors—which means that cannabinoid receptors are instrumental in regulating bone density.

Other experiments would establish that CB receptor signaling modulates pain and analgesia, inflammation, appetite, gastrointestinal motility, neuroprotection and neuroregeneration, along with the ebb and flow of immune cells, hormones, and other mood-altering neurotransmitters such as serotonin, dopamine, and norepinephrine. When tickled by THC or its endogenous cousins, cannabinoid receptors trigger a cascade of biochemical changes on a cellular level that put the brakes on excessive physiological activity.

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 misfires, if the pilot light burns too high, if the immune system goes into overdrive, the body's homeostasis is compromised and the stage is set for an autoimmune disease or an inflammatory disorder to develop.

Endocannabinoids are the only neurotransmitters known to engage in "retrograde sig- naling," a unique form of intracellular communication that inhibits immune response, reduces inflammation, relieves muscleatrophy, lowers blood pressure, dilates bronchial pas- sages, increases cerebral blood flow (a rush of thoughts!), and normalizes overstressed nerves. Retrograde signaling serves as an inhibitory feedback mechanism that tells other neurotransmitters to cool it when they are firing too fast.

A German research team would later demonstrate that CB-2 receptor activation restrains the formation of bone reabsorbing cells, known as osteoclasts, by down-regulating osteo- clast precursors, thus tipping the balance in favor of osteoblasts, cells that facilitate bone formation.

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. Endo- cannabinoidase-related enzymes are known to inhibit immune response, reduces inflammation, relieves muscleatrophy, lowers blood pressure, dilates bronchial passages, increases cerebral blood flow (a rush of thoughts!), and normalizes overstressed nerves. Retrograde signaling serves as an inhibitory feedback mechanism that tells other neurotransmitters to cool it when they are firing too fast.

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High-endocannabinoid levels in the brain are triggered by strokes and other pathological events—attesting to the neuroprotective function of the endocannabinoid system. A major function of the endocannabinoid system—and therefore a significant effect of the cannabinoids in marijuana—is neuroprotective in nature: protecting brain cells from too much excitotoxicity. The endocannabinoid system, according to Mechoulam, is part of the body's "general protective network, working in conjunction with the immune system and vari- ous other physiological systems." His discoveries posed a direct challenge to sci- entific orthodoxy by revealing that the brain has a natural repair kit, an in-built mechanism of protection and repair, which can mediate damaged nerve and brain cell health.

Ironically, the U.S. government's unending search for marijuana's harmful properties yielded astonishing scientific insights that validated the herb's therapeutic utility. By stimulating CB-1 and CB-2 receptor signaling, marijuana functions as a substitute "retro- grade messenger" that mimics the way our bodies try to maintain balance. Cannabis is a unique herbal medicine that taps into how our bodies work naturally. Thanks to this plant, scientists have been able to decipher the primordial language that nerve and brain cells use to communicate. From womb to tomb, across countless generations, the endo- cannabinoid system guides and protects.

But a big disconnect existed between the world of science and the general public. Aside from certain segments of the scientific community, few people knew about the endocannabi- noid system. Doctors, journalists, public officials—hardly anyone was clued in to the unique herbal medicine that taps into how our bodies work naturally. Thanks to this plant, cannabinoid compounds could induce apoptosis (cell death) in cancer cells without washing the whole body.

Guzmán and his colleagues confirmed that THC and its synthetic emulators selectively killed cancer cells while leaving healthy cells unscathed. No Big Pharma chemotherapeutic drugs could induce apoptosis (cell death) in cancer cells without washing the whole body. Up to 90 percent of advanced cancer patients suffer cognitive dysfunction from "chemo brain," a common side effect of corporate cancer meds that indiscriminately destroy brain tissue while leaving cancer cells unscathed. Therapies like CBD and CB-2 agonist, cannabinoid drug treatments could induce apoptosis (cell death) in cancer cells without washing the whole body.

There is mounting evidence that cannabinoids may "represent a new class of anticancer drugs that retard cancer growth, inhibit angiogenesis [the formation of new blood vessels] in tumors, and metastatic activity of cancer cells," according to scientific review in Journal of Medicinal Chemistry. Studies from scientists around the world have documented the anticancer properties of cannabinoid compounds for various malignancies, including (but not limited to):

- Breast cancer.
- Pancreatic cancer.
- Colon cancer.
- Cervical cancer.
- Lung cancer.
- Stomach cancer.
- Breast cancer.
- Pancreatic cancer.
- Colon cancer.
- Cervical cancer.
- Lung cancer.
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