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Timmen L. Cermak
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Section 1 The Science of Marijuana and the Brain

Chapter 1

Monumental Marijuana Discoveries

The discovery of cannabinoid chemistry began with Raphael Mechoulam, born in Sofia, Bulgaria in 1930. Anti-Semitism stripped Mechoulam's father of his hospital leadership and sent him to a lesser position outside Sofia, and then to a Nazi concentration camp. After his surviving the camp, the family immigrated to Israel in 1949 when persecution continued after World War II under communist rule.

Mechoulam's interest in chemistry led to his being assigned to an Israeli army unit researching pesticides. This experience began a lifelong pursuit of the "sweet taste of research," which he called "an addiction from which I do not want to be cured."[1]

Returning from postdoctoral studies at the Rockefeller Institute in New York in the early 1960s to a junior faculty position at the Weizmann Institute of Science in Rehovot, Israel, Mechoulam began looking for an "important topic" to begin his research career. He was especially fascinated by the interaction of chemistry and biology and saw a ripe opportunity with marijuana. While morphine had been isolated and identified as the most active compound in opium (the gummy harvest from immature poppy seed pods) 150 years before, and cocaine had been isolated from coca leaves 100 years before, the active component of marijuana was still unknown. It had not yet been isolated in pure form, its structure had not been identified, and essentially no one else was working on it at the time. Here was a mystery waiting to be solved, and a young researcher looking to make his mark was just the person to solve it.

Raphi, as colleagues often call him, still enjoys telling how his grant proposal to study marijuana was rejected by the U.S. National Institute of Health (NIH) on the grounds that, according to the NIH, "Marijuana is not an American problem." He was told to return with a request for funds when he found "something relevant" to research. One year later, Mechoulam recounts with amusement, the head of pharmacology at NIH, Dan Efron, traveled to Israel to meet with him. Apparently, a U.S. Senator had

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caught his son smoking pot and called Efron to ask if it was destroying his son's brain. In Mechoulam's words, NIH knew they "didn't have the foggiest idea what marijuana does." By that time Mechoulam and his team had painstakingly isolated the active ingredient in marijuana – THC. Efron flew back to NIH with 10 grams of the purified extract in his pocket and Mechoulam received NIH funding for the next four decades without any interference in his research by our government.

Mechoulam's team published the first report of successful isolation and identification of THC with proof it was the primary psychoactive component of marijuana in 1964.[2] Two factors aided this discovery: first, the recent development of more powerful instruments for separating THC from the profusion of other chemicals in marijuana, including many that closely resemble THC, and then identifying its structure, and second, the convenience of working in a small country.

In order to isolate THC, Mechoulam needed a good supply of marijuana or hashish. Naïve about how to get enough raw material to work with, Mechoulam asked the director of the Weizmann Institute for help. A call to the director's old army buddy at police headquarters in Tel Aviv to vouch for the young professor's reliability quickly secured five kilograms (11 pounds!) of superb hashish that had been captured from Lebanese smugglers. Not having a car, Mechoulam took a bus to Tel Aviv to retrieve the hashish. By the time he completed the 17 miles back to Rehovot, fellow bus passengers were trying to figure out the strange odor coming from his bag. When he later realized he had broken the law by not first obtaining a permit from the Ministry of Health, Mechoulam apologized at the ministry in person. Many officials at the ministry were his former students and, after giving him a gentle scolding, they quickly forgave his transgression. With the ministry's written permission from that point forward, Mechoulam continued to obtain marijuana and hashish from the police for over 40 years.

Mechoulam and Yehiel Gaoni, an organic chemist, began searching for the active component in hashish by extracting its oils with a highly volatile hydrocarbon solvent. They then separated the over 400 compounds in the extract by repeatedly pouring it through a glass tube filled with aluminum oxide. Different oils ran through the tube at different speeds, which enabled researchers to separate each by collecting filtrates at different times. A colleague administered each of the different oils to rhesus monkeys and only one oil caused the same sedation known to be produced by marijuana. Ten members of Mechoulam's research team participated in a blind study with half getting the same oil as the monkeys and half getting a placebo. It was immediately apparent that those getting the active oil were affected quite differently than those getting the placebo. Some felt "weird," some felt nothing but talked or laughed a great deal, and one became visibly anxious. Those who were familiar with the effects of marijuana recognized that the oil they had extracted from hashish felt similar. At that point Mechoulam's team had isolated the active component in the cannabis plant, but what exactly was it?

The structure of this active component was determined by using the same principle as medical Magnetic Resonance Imaging (MRI) scans, which generate a strong magnetic field to analyze the resonance of hydrogen atoms to form images of structures in the body. Chemists use a mass spectrometer with a wide spectrum of magnetic frequencies to identify the different atoms in complex molecules. The active component in Mechoulam's psychoactive extract from hashish, called delta-9-tetrahydrocannabinol (THC) (Figure 1.1), had the following structure:

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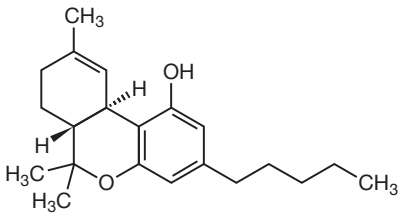

Figure 1.1 The structure of delta-9-tetrahydrocannabinol.

Discovering the structure of THC was important. Scientists could now synthesize the compound in its pure form, which was a lot easier than separating it from other molecules by the tedious chromatography process of repeatedly pouring cannabis oil through a column and catching what dripped out at precisely the same time each trial. Not only could Mechoulam now synthesize THC, but he also incidentally noted that THC's structure had much in common with a fatty acid (arachidonic acid) found in all cell membranes – an observation that became highly relevant 20 years later. Chemists around the world began modifying the basic THC molecule to form new analogs – that is, chemical compounds that are structurally similar but differ slightly in their composition. The world of synthetic cannabinoids was born in laboratories for research purposes. For example, in 1974, Pfizer Pharmaceutical created CP-55,940, a compound 45 times more potent than THC that subsequently contributed to further important cannabinoid research. Clemson's John W. Huffman developed a series of numbered compounds beginning with his initials, JWH, while Mechoulam contributed HU-210 (which is 100 times stronger than THC) – all for the purpose of furthering research into how THC affects the brain. Synthetic cannabinoids produced in laboratories and not found in the cannabis plant clearly represented new, more powerful, and potentially riskier drugs if used recreationally. Unfortunately, several synthetics have been pirated from laboratories, sprinkled on innocuous herbs such as oregano, and sold under brand names such as Spice and K2. These powerful synthetic cannabinoids can do serious harm requiring emergency medical care, including extreme anxiety, confusion, and paranoia.

The next couple of decades were busy for Raphael Mechoulam as he continued to explore the chemistry contained in cannabis plants, a new branch of research that he called "cannabinoid chemistry." He participated in multiple studies researching the potential medical benefits of marijuana's compounds, especially of CBD, the structure of which he had characterized the year before his discovery of THC.[3] But the biggest mystery was still unsolved: how did THC interact with the brain to produce its effects? There were some indications that it produced changes in cells similar to those seen with molecules for which unique receptor sites were present, but undetected impurities in THC's synthesis complicated this line of thinking. At the same time, others argued that the fat-soluble nature of oily THC resembles common anesthetics that work by dissolving into the fatty membranes of nerve cells and interfering with conduction of electrical impulses.

There was little benefit in knowing the bare fact that THC is the chemical in marijuana most responsible for getting people high. Being able to repeat an impressively long chemical name – delta-9-tetrahydrocannabinol – does not really bring anyone closer to understanding how marijuana works. A central mystery remained until the mechanism by which THC interacts with the brain and alters its function was discovered.

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The next monumental breakthrough came in 1988 from researchers at St. Louis University Medical School. Allyn Howlett and a graduate student, William Devane, announced the discovery of a unique, cannabinoid-specific receptor in the rat brain.[4] While THC can be labeled radioactively, it does not bind tightly enough to this receptor to be a useful probe. By using radioactively labeled CP-55,940, Pfizer's powerful synthetic cannabinoid with more intense affinity for the receptor, they demonstrated that cannabinoid molecules attach to very specific receptor sites that naturally occur in the brain. Howlett and Devane had discovered a clearly defined cellular mechanism to explain interaction between cannabinoid chemistry and biophysiology – the direct linkage between marijuana and the brain!

The mechanism of chemical communication between nerve cells (called neurons) is as remarkable as any of nature's many wonders. Receptors for neurochemicals are complex proteins, over 400 amino acids long, that naturally fold up on themselves multiple times and then float in the thin fatty membrane that encases cells. Each typical receptor crosses the cell membrane seven times, with portions sticking up outside the cell and other portions entering into the cell's interior. The analogy of neuroreceptors to locks that can be opened only by specific keys is quite apt, though an oversimplification, as will be discussed in Chapter 10. Our nervous system brings "keys" (neurotransmitter molecules) and "locks" (receptor sites) together in what are called synapses. Synapses generally consist of an upstream neuron's passing its neurotransmitter across a short distance (20–40 nanometers) to a downstream neuron's receptor sites. For example, when a neurotransmitter such as serotonin or dopamine is released by an electric impulse travelling from a neuron cell body down its long extension (axon) to a synapse, the neurochemical crosses the synapse and slips into its unique receptor site in the next neuron downstream. Like a key opening a lock, the neurotransmitter alters the receptor's shape. This change in the receptor's conformation then allows the passage of ions (typically calcium) into the cell to activate complex events that either stimulate or inhibit its activity. The pattern of stimulation and inhibition passing through the brain from one neuron to another creates a stream of information much like the stream of electric impulses in a computer. The exquisite level of detail being transferred through the brain can literally be *seen* by focusing attention on the dynamic wealth of visual information being passed from your retinas to the back of your brain and then into conscious awareness of whatever you are seeing at any moment. The remarkable speed and detail of neuronal impulses and synaptic activity occurring in the brain can be experienced directly, though we generally take all this for granted.

Howlett and Devane solved the mystery of how THC interacts with the brain when they discovered cannabinoid-specific receptors. In an extreme understatement, they ended the article announcing their discovery by saying, "Thus, the importance of the characterization of a cannabinoid receptor will make a major impact on research in this field."[5] In fact, the cannabinoid receptor they discovered was soon recognized to be the most abundant neuroreceptor in the brain.[6] Neuroscience researchers around the world responded to Howlett and Devane's discovery like thoroughbreds when the bell rings and the gates open at a racetrack.

Since it was highly unlikely that evolution had developed cannabinoid receptors solely for the purpose of responding to marijuana's THC, the horse race to discover the brain's natural cannabinoid neurotransmitter had begun. Mechoulam described his

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response to Howlett and Devane's discovery by saying, "We assumed that a cannabinoid receptor is not formed for the sake of a plant that has compounds that bind to it, but for an endogenous [naturally occurring] brain . . . [compound]. I decided to try to identify it."[7] He also recruited William Devane to work at his laboratory at Hebrew University and teamed him with Lumir Hanus, a visiting Czech chemist.

Two important pieces of research in the U.S. were reported by the NIH in 1990 while Mechoulam's team was hard at work trying to isolate the brain's natural cannabinoid. Early in the year, Miles Herkenham reported using radioactively labeled CP-55,940 to map the location of cannabinoid receptors.[8] He soaked slices of brain from several mammalian species (including human) in a solution containing the radioactive cannabinoid and then spread the slices out on radioactive-sensitive film. When he developed the film three to four weeks later, Herkenham had images of where cannabinoid receptors are most densely concentrated. Several conclusions were immediately apparent: first, there was a huge number of cannabinoid receptors in the brain; second, their unique distribution was the same across several different species; and third, by matching an area of the brain that is densely populated by cannabinoid receptors with the mental functions known to be related to that specific area (for example, the hippocampus and memory), we can begin understanding why marijuana produces its unique effects (explored in detail in the next chapter). Herkenham had mapped the brain areas that give rise to pot's characteristic high when stimulated by THC. He also observed that "sparse densities in lower brainstem areas controlling cardiovascular and respiratory functions may explain why high doses of delta-9-tetrahydrocannabinol are not lethal."[9] In other words, pot does not interfere with breathing like opiates do, too often with fatal consequences.

The other discovery at NIH in late 1990 involved cloning the cannabinoid receptor by Lisa Matsuda.[10] Her work demonstrated that human chromosomes possess the DNA for building cannabinoid receptors and she described the receptor's exact structure. By cloning the DNA, she enabled researchers to produce cannabinoid receptors in unlimited numbers, which facilitated searching for natural cannabinoid compounds in the brain that would activate these receptors. The hunt was circling more tightly on a possible endogenous (i.e., produced within) cannabinoid in the brain.

To anyone who had followed the endorphin story, the trail of research involving cannabis looked familiar. In both cases – poppies and cannabis – the active mind-altering ingredients were purified from plants and radioactively labeled to search for receptors in the brain. In the case of poppies, researchers soon found opiate receptors and endogenous morphine-like neurotransmitters (endorphins, for short) produced by the brain. An entire endorphin *system* exists, including receptors and all the enzymes needed to synthesize and metabolize natural opiate neurotransmitters. It was growing apparent that the same was also being found to be true for an endogenous cannabinoid (endocannabinoid, for short) system. Both Herkenham and Matsuda explicitly referred to this likelihood in their papers, and Mechoulam's laboratory was about to verify this reality.

Raphi's "mixed bag"[11] of researchers at Hebrew University of Jerusalem, "Moslem and Christian Arabs, observant and non-observant Jews . . . a German and an American" (William Devane) published a report of the first isolation of the brain's natural cannabinoid in 1992.[12] Devane was studying Sanskrit at the time and chose the name "anandamide," which means "supreme joy, or bliss." Mechoulam explained their choice of the

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name as being one that only a dedicated laboratory researcher might make when feeling the special joy of being the first to make a significant scientific discovery. "We were quite happy to discover the compound," he said in a gross understatement. And he joked that they did not use a Hebrew name "because in Hebrew there are not so many words for happiness . . ."[13]

Isolation of the first brain cannabinoid, anandamide, identification of its structure, and confirmation of its cannabinoid properties required expertise in multiple disciplines, which illustrates the need for a team of diverse researchers. They first developed a unique radioactively labeled synthetic cannabinoid and mixed it with synapses containing cannabinoid receptors concentrated from rat brains. The question was: could they extract anything from brains to add to the solution of synapses that would bind to the cannabinoid receptors and thus leave fewer open receptor sites for the radioactive cannabinoid to attach to? If less radioactively labeled cannabinoid was able to bind with receptors already occupied by the natural cannabinoid they had extracted, it would be washed out and the total radioactivity of the solution would be reduced. The team knew the endocannabinoid they were looking for would be a fatty substance and searched for the lipid using a technique called thin-layer chromatography (TLC). The principle of TLC can be seen whenever you splatter grease on a nice shirt and it begins spreading out from where it first landed. Since different compounds "travel" at different speeds, Mechoulam's team was able to separate lipids from ground up pig brains into finer and finer extracts. By a process of successive approximations, they continued to concentrate the portion that competed with the radioactive synthetic cannabinoid for cannabinoid receptors. In the end, 4.5 kilograms (almost 10 pounds) of brain yielded 0.6 mg (0.000021 ounces) of the substance they called anandamide – the first natural endocannabinoid discovered (others soon followed, though with more mundane names, e.g., 2-AG).

A new chapter in marijuana research dawned with the discovery of anandamide, and research interests split into two parallel, only partially overlapping paths. Basic neuroscience researchers explored one path by focusing on the brain itself. They investigated the role this newly discovered endocannabinoid system plays in normal brain function. What does the endocannabinoid system contribute to the body's normal physiology? Why does our DNA contain instructions for enzymes to synthesize and metabolize anandamide and to build natural cannabinoid receptors? While fascinating basic discoveries have poured into the neuroscience literature, far more questions have been generated than answers. Basic research into the endocannabinoid system will remain on the exciting cutting edge of neuroscience for the next few decades.

Researchers primarily interested in marijuana took a different path. They focused on the remarkable similarity in the three-dimensional structures of anandamide and THC. The U.S. National Institute of Drug Abuse (NIDA) provided a dramatic comparison of the two molecules on its website (www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects) (Figure 1.2).

Researchers immediately understood that marijuana affects our brain because the THC it contains is a great mimicker of endogenous cannabinoids. The brain cannot distinguish between the THC in marijuana and its own natural cannabinoid chemistry, which forms the basis for both recreational and medicinal marijuana use.

On the recreational side, researchers focused on the human consumption of marijuana and began eagerly exploring what happens when THC activates our

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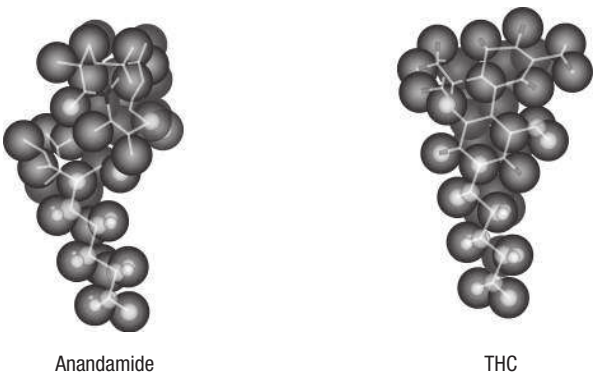

Figure 1.2 Comparison of anandamide and THC molecular structure. Source: NIDA. www.drugabuse.gov/publications/research-reports/marijuana/how-does-marijuana-produce-its-effects.

endocannabinoid system. Exactly how do molecular events result in the cannabinoid experience of being high? Once THC fits into receptors designed by evolution for anandamide, does it unlock the receptor any differently than anandamide, any wider, or longer? And what are the consequences of consistently activating our cannabinoid system with THC weekly, twice a week, or even daily?

On the medicinal side, researchers wondered how modifying endocannabinoid activity reduces pain and suffering, and even treats some human diseases. They began taking their lead from folk medicine and anecdotes about marijuana's medicinal benefits. First, researchers put these claims to the test by applying the scientific method to move from mere opinion to objective, reproducible fact. Second, as basic research better understood our endocannabinoid system, research could begin exploring the mechanisms by which the chemistry in marijuana exerts its beneficial effects, as well as its negative side effects.

Before the impact of marijuana on the brain, whether used recreationally or medically, can be explored further, some necessary additional detail about the uniquely central role the natural endocannabinoid system plays in regulating brain function must be understood. The discovery of an entire endocannabinoid *system*, composed of neurotransmitters and receptors, ignited an international explosion of neuroscience research. In 1993, Sean Munro at the University of Cambridge, UK, discovered a second cannabinoid receptor in the rat spleen, with no evidence of its presence in the brain.[14] The original receptor identified in 1988 by Howlett and Devane now became referred to as the CB1 receptor. Because CB1 receptors are found primarily in the brain and the newly discovered CB2 receptors are found primarily in the immune system and other parts of the body, the two began being called central and peripheral cannabinoid receptors respectively, though later research has found CB2 receptors in the brain under some conditions.

The following year, Vincenzo Di Marzo in Paris and colleagues in Italy and California reported that anandamide is produced from a precursor present in all cell walls – the polyunsaturated fatty arachidonic acid.[15] Like Mechoulam, Di Marzo had immediately recognized the chemical structure of anandamide closely resembles this ubiquitous building block for the lipid membrane surrounding cells. Cell membranes are essentially films of fatty acids. Oil and water do not mix, so a fatty membrane is an effective barrier for separating the watery inside cells from the watery outside. The existence of

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anandamide's precursor in cell membranes is distinctly different from how neurotransmitters are typically formed and stored. Neurotransmitters such as serotonin, GABA, and dopamine are synthesized in the neuron cell body far from where they are released. After synthesis they must first be transported through the cell's axon to be stored near synaptic connections with other neurons. Small electrical disturbances running down the axon's outer membrane trigger release of the neurotransmitter into the synapse. We typically say that the neurotransmitter is released when a neuron "fires."

Di Marzo's investigation of neurons in culture found that anandamide is synthesized from the arachidonic acid in cell membranes in response to calcium ions that typically flow into cells through receptor sites unlocked and opened by their unique transmitter molecule. A variety of typical neurotransmitters locking into their receptors were all found to activate the synthesis of anandamide from the arachidonic acid in cell membranes. The life span of anandamide once released into the synaptic space outside the cell is short due to rapid cellular reuptake and degradation. Di Marzo concluded that anandamide's action within the brain depended on its reaching cannabinoid receptors located somewhere on neighboring cells. The exact location of this interaction between endocannabinoid and CB1 receptors was still unknown.

While Di Marzo was investigating the synthesis of anandamide, Mechoulam's exploration of the newly identified peripheral CB2 cannabinoid receptor discovered a second endocannabinoid in 1995 – 2-arachidonyl glycerol (2-AG).[16] Reasoning from the existence of several peripheral cannabinoid effects (e.g., bronchodilation, decreased intraocular pressure, and intestinal calming), Mechoulam assumed that endocannabinoids would be found in both brain and the rest of the body. After extracting 2-AG from dog intestines, he demonstrated that it satisfied the cannabinoid tetrad when administered to animals, i.e., decreased spontaneous activity, pain reduction, lowered temperature, and immobility. Furthermore, anandamide was absent in the gut extract. The endocannabinoid system, now consisting of at least two different receptors and two different neurotransmitters (there would eventually be more), was rapidly growing in complexity. By 1997, Nephi Stella, a postdoctoral fellow at the Neurosciences Institute in San Diego announced that 2-AG exists in the brain as well and measured it in amounts 170 times that of the more poetically named anandamide.[17] Exploration of our brain's endocannabinoid system was rapidly picking up speed.

While understanding that an endogenous cannabinoid system exists within the brain and is stimulated by THC's similarity to our natural neurochemistry is important information for health professionals to master, there are a few more essential characteristics of this fascinating system to be understood. At this point many clinicians may fear I am about to get lost in the basic science weeds, so to speak, but I ask readers' forbearance. One more monumental discovery wraps the preceding basic science into a coherent whole with profound implications. Integrating the following information will provide an understanding of how the endocannabinoid system regulates the rest of brain chemistry.

The expanding international scope of research is illustrated by the next stop in the endocannabinoid story – Hungary. Mechoulam's laboratory had discovered anandamide five years before Istvan Katona began his Ph.D. studies at Semmelweis Medical University in Budapest. Katona had attended the prestigious Trefort high school (alma mater of the theoretical physicist Edward Teller, developer of the hydrogen bomb) where university students did their practice teaching. Raised during the communist occupation

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of Hungary, Katona pursued a scientific career "because it provided the luxury of intellectual freedom."[18] The newly described endocannabinoid system was the hot topic for neuroscience graduate students needing to make their mark in research. Katona began exploring the microanatomy of this new system and made his mark with a series of groundbreaking papers beginning in 1999.[19]

Neurons are essentially one-celled animals that live throughout an organism's lifetime. Some stretch from the base of our spine down to the end of our toes, over a meter long in very tall people. They can survive independently in a petri dish when given the proper nutrients. The brain is made up of approximately 86 billion of these one-celled animals – quite a can of worms. What makes neurons unique among all our body's different cell types is their ability to communicate with each other and to form complex interconnected networks.

Communication occurs when a presynaptic neuron passes a chemical messenger to receptors on the next postsynaptic neuron. These one-way synaptic connections pass signals along from neuron to neuron to neuron. There are a nearly inconceivable number of synapses in the human brain – roughly 5000 times as many as there are stars in our Milky Way galaxy. The predominant flow of information throughout the brain occurs by passing chemical messengers downstream across synapses from one separate neuron to the next.

Istvan Katona's contribution was to localize endocannabinoid receptors, not just where they are found in the brain (Miles Herkenham had done this), but also more specifically where they exist on each neuron. He argued that this was the only way to know the mechanism of action of both marijuana's THC and the brain's natural cannabinoid chemical messengers. He followed a path suggested by two pieces of research. First, it has long been known that a brain area shaped like a seahorse called the hippocampus is crucial to learning and memory. The hippocampus is the scratch pad substrate for our short-term memory. It creates a neural model for information that is then uploaded into longer memory storage. Without a functioning hippocampus, no memories are stored – a condition called Korsakoff's Syndrome seen in end stage alcoholism. A temporary functional Korsakoff's is experienced when binge drinkers "blackout" and have no memory the next morning for the night before. While marijuana users do not experience anything as extreme as blackouts, they do commonly experience difficulty with short-term memory. Careful cognitive studies, reviewed in detail in a later chapter, have documented the reality of learning and memory decrements during THC intoxication. The second piece of research was Herkenham's work showing a very heavy concentration of CB1 receptors in the hippocampus. Where there is smoke, Katona hypothesized, there may be interesting fire.

Katona used electron microscopy to examine hippocampal slices stained with gold-labeled antibodies to CB1 receptors and found that the gold particles were located *pre*synaptically, not *post*synaptically as typical receptors are. He describes the moment of discovery as "fantastic, I will never forget seeing [the receptors] in the electron microscope, it was indeed a Eureka moment, which made me addicted to neuroscience research."[20] His words echo Rafael Mechoulam's bliss at discovering anandamide – the profound joy and awe of being the first human to observe one of nature's previously hidden secrets!

The presynaptic location of CB1 receptors means that the endocannabinoid system is not structured to pass information downstream from one neuron to the next, but rather

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to provide feedback to upstream neurons. This simple fact turns everything about the endocannabinoid system on its head and makes sense of Di Marzo's discovery that activation of a variety of receptors by their corresponding neurotransmitters sets the synthesis and release of anandamide in motion. The endocannabinoid system is not simply one more typical neurotransmitter system. The endocannabinoid system does not fit the usual model for passing information downstream from one neuron to the next.

Katona's research went a step further in describing the functional impact of the presynaptic location of CB1 receptors. Electrical stimulation in the hippocampus of the presynaptic neurons upon which the CB1 receptors were located led to the release of the neurotransmitter called GABA. When Katona activated the CB1 receptors with a powerful synthetic cannabinoid (WIN 55,212), electrical stimulation no longer released the GABA. To be sure that cannabinoid stimulation was the direct cause of turning off the GABA neuron, he repeated the experiment after pretreating the CB1 receptors with a recently developed cannabinoid blocker SR141716. Once CB1 receptors were blocked, WIN 55,212 could no longer activate them, and electrical stimulation again released GABA.

While the research described above may be confusing, and more detailed than most need to remember, the conclusions Katona reached should be clear. *The endocannabinoid system acts as a negative feedback system designed to modulate nearly all the other neurotransmitters in the brain.*[21] CB1 receptors in the brain consistently appear to be presynaptic and "activation of presynaptic, CB1 receptors always results in the attenuation of neurotransmitter release."[22,23] In a 2008 paper Katona and Tamas Freund elaborated on this idea by describing the function of the endocannabinoid system as a "circuit breaker" in the brain.

The endocannabinoid system is fundamentally a neural homeostatic mechanism. Homeostasis simply means that biology has provided us with multiple ways of maintaining a constant internal environment. For example, if we get too hot, we perspire to cool ourselves. If we drink too much water, we urinate more. In the case of brain activity, if a neuron gets too active and releases large enough amounts of neurotransmitter, negative feedback by the endocannabinoid system reduces the amount released by the presynaptic neuron. Our natural cannabinoid system works to stabilize brain activity. While this sounds good, and maybe even sounds like a reason to consume the phytocannabinoids offered by marijuana, the story is never that simple when dealing with biology. Complications caused by external stimulation of the endocannabinoid system by marijuana use, especially on a regular basis, will be reviewed in later chapters.

The endocannabinoid system needs to be seen as always active to one degree or another. Like a dripping faucet, the activity is either increased or decreased in response to the level of presynaptic neuronal activity. In other words, our endocannabinoid system is a "tonic" system – it has a tone (similar to a muscle's tone) that can be altered. The normal, physiological stimulus for altering endocannabinoid tone is the release of neurotransmitters from a presynaptic neuron. Activity produced within the postsynaptic neuron by arrival of the neurotransmitter (i.e., influx of calcium ions) initiates the synthesis of anandamide and 2-AG from the lipids in the cell membrane. Although enzymes begin breaking them back into their components soon after synthesis and release, if the presynaptic neuron is firing rapidly, enough endocannabinoids are produced that some diffuse back across the synapse and reach the presynaptic CB1 receptors. When the cannabinoid receptors are activated, they initiate events within the presynaptic

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