# Another Year Goes To Pot: Cannabis Science 2006

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## INTRODUCTION

The cannabis plant is an amazing source of medicinal chemicals, the reason being it is the only plant that truly taps into our endocannabinoid system. While marijuana has been used medicinally for thousands of years, it is only within the past fifteen years that we have begun to understand why marijuana has so many medicinal properties. As a result, research into this area has exploded. One cannot understand medical marijuana without first understanding the endocannabinoid system and the fundamental role that it plays in the lives of all animals, especially man.
The endocannabinoid system is composed of receptors (CB1-nervous system and CB2-immune system) on cells that bind exocannabinoids like THC, and endocannabinoids that our bodies produce, like anandamide (AEA) and 2-arachidonyl glycerol (2AG). Both of the latter chemicals are made from essential fatty acids such as are found in hemp oil. When cannabinoid receptors are activated, various biochemical properties in cells are altered, and these cells then alter communication with other cells. However, all body systems must be regulated, therefore, enzymes exist that break down our endocannabinoids to keep this system in balance (homeostasis, see below). The most studied enzyme that breaks down some endocannabinoids is fatty acid amino hydrolase (FAAH). Specifically, FAAH breaks down anandamide, thereby decreasing endocannabinoid activity. In order to really appreciate the medicinal properties of this plant, we must understand the basic properties of life itself. How ironic, after so many cannabis users have been persecuted for believing that marijuana is the tree of life, in many respects it is.

## CREATIVE ENERGY FLOW-LIFE

For the first time in the history of mankind, we can look at life from a truly scientific prospective and understand its basic properties. We will not go into the details of the physics of life, but rather we will describe some of the basic characteristics of life from the perspective of far from equilibrium thermodynamics. For our purposes, these ominous terms can be easily understood. Let’s start with equilibrium. Scientifically, equilibrium is a state of maximum disorder (entropy), and simultaneously, a state of minimum potential (the ability to do something). In other words, equilibrium is the opposite of life. Thermodynamics refers to the flow of energy. It is, in fact, this flow that keeps life away from equilibrium. The movement towards equilibrium is characterized by

aging, illness and death. On an organismic level, living systems maintain the critical flow of organizing energy by eating, sensing the environment, and getting rid of waste products. However, the same principle of extracting potential from the environment is true at the cellular level.
A unique characteristic of matter driven further from equilibrium, is that it possesses a natural tendency to create new forms of organization. From the human prospective, moving further from equilibrium can mean regaining one's health and increasing one's organization and energy flow (as occurs with physical training). Similarly, learning and enhanced thinking skills (such as state of mind) can represent movement from equilibrium. Another irony, our cannabinoid system is totally intertwined with these processes.

## HOMEOSTASIS

In the biosphere, the creative process is evolution. As evolution proceeds, we see increasing complexity, a property most obviously characteristic of man and his society. However, this complexity is not only between man and his environment, but within man himself, existing at all levels of organization. Before going further into the endocannabinoid system and the impact of marijuana on it, a critical term that we must understand is homeostasis. It essentially means biochemical balance, but dynamic balance not static balance. A simplistic visual image of the dynamic character of biochemical homeostasis would be a bunch of jugglers balanced on a bunch of seesaws that are balanced on each other, while moving on a roller-coaster ride. The level of complexity in this seemingly impossible task is readily accomplished biochemically by living organisms all the time. In fact, the endocannabinoid system plays a critical role in coordinating the many balancing acts associated with life and does so across scales of organization. The impact of cannabinoids ranges in scale from controlling biochemistry within cells to controlling social interactions and regulating political thought [1].

## EMERGENT PHENOMENA

Another fundamental characteristic of living systems is that the whole is greater than the sum of its parts. Pieces of a system work together and create something new and different, something that would not have been predicted from observing the individual components in isolation. How does this phenomenon impact on the health of cells, individuals, communities and society, and is the role cannabinoid system? Is consciousness an emergent phenomenon, with the cannabinoid system being a critical player in the emergence process?
Before we look at the endocannabinoid system, let's restate some of the physics of life. All foods provide us with building blocks and the energy necessary for organizing the building process. The chemicals that we call food can be viewed as charged batteries. They have potential to do things such as promoting growth, health and evolution. Energy flow in a living system is similar to what occurs when a battery is used to do something. In both cases, energy comes from the flow of electrons. Living systems are essentially rechargeable, biochemical batteries, and our biochemical pathways constitute the wires.

Without going into details, the flow of biochemical electricity produces free radicals, biochemical friction.

## FREE RADICALS

Free radicals are highly reactive chemicals that modify life's chemicals. Free radicals have three critical biological functions. On the one hand, due to their reactivity, free radicals alter the chemical properties of DNA, RNA, proteins, carbohydrates and fats. By doing so, they disrupt biochemical organization. Therefore, the destructive nature of free radicals may be viewed as the friction of life. On the other hand, as a result of free radical-induced biochemical modifications, free radicals serve to signal the cell that all is not right, either with respect to energy flow from environmental, and/or the internal energy flows (such as mental stress). Thirdly, the destructive power of free radicals has been harnessed by the immune system to help destroy infectious invaders. Immune cells actually make hydrogen peroxide and the chemical equivalent of Clorox to help kill pathogens.

## EVOLUTION

Over 500 million years ago, cells began to communicate with one another and to develop new levels of cooperation that, in turn, allowed for increased levels of complexity (spatially, temporally, and physically). These primitive, communicating, multi-cellular organisms began the evolutionary process that lead to the body systems that we're familiar with today: circulatory, digestive, endocrine, immunological, musculoskeletal, nervous, reproductive, respiratory and tegumentary (skin). Interestingly, it was at this critical time in life's history that the endocannabinoid system had its origins and found its place as a critical modulator of biological activities. As evolution proceeded, and systems and their interactions grew more complicated, the endocannabinoid system increasingly played an important role in the dynamic balancing acts that characterize not only life, but also economic, social, political, and religious institutions. As our understanding of the magnitude and diversity of cannabinoid biology increases, it naturally extends beyond the biological realm through its regulation of complex human behavior.
All cells exhibit basic biological properties. Typically they are replicating, performing some differentiation related task, resting or dying, all the while communicating with their neighbors, ideally, for the good of the organism as a whole. Cannabinoids regulate all of these basic activities as a function of cell type, dose, etc. What are the implications of this broad cannabinoid based activity that spans from sub-cellular activities to consciousness and beyond? We will examine some of the cannabinoid-based scientific discoveries that occurred in 2006 and see what picture is painted regarding the essential role of cannabinoids in human health.

## SCIENCE NOT POLITICS

First, let's clarify our starting point. Cannabis plant material is highly variable in composition. Therefore, even in the absence of governmental interference, the plant material is not ideally suited for most scientific experimental studies (which need not

limit its medicinal usefulness). Accurate dosing and reproducibility are critical components of scientific inquiry. These constraints are met experimentally by using agonists, chemicals that stimulate specifically the CB1 or CB2 receptors, and antagonists, chemicals that inhibit specifically the CB1 or CB2 receptors. Today, we know that many of the activities produced by cannabinoids occur via cannabinoid receptor independent mechanisms, further demonstrating how complex cannabinoid activities are. In addition to the new synthetic cannabinoids, naturally occurring THC and CBD are often used experimentally. Thus, we mostly learn about the cannabinoid system without actually using products isolated from the cannabis plant. When the science and observations of medical marijuana users are put together, the benefits of medical marijuana should be obvious to all.

**NERVOUS SYSTEM**

A good place to begin examining cannabinoid discoveries of 2006 is the nervous system. Current knowledge clearly shows that the brain has robust regenerative capacities. One of the newly discovered surprises is that nerve regeneration, that develops from neural progenitor cells, is regulated by endocannabinoids [2]. In other words, when there is brain injury, as occurs from head injury or stroke, the brain produces marijuana-like compounds [3] that are important limiters of damage and promoters of healing.

The ability to feel pain is a critical biological response to injury (it helps us avoid it). We now know that the level of cannabinoid receptors is turned up in response to chronic inflammation and its associated pain. The body, apparently in effort to reduce pain [4], enhances endocannabinoid activity. This response is not surprising since endocannabinoids are direct regulators of pain receptors [5].

Superoxide dismutase (SOD) is an enzyme that helps protect cells against free radical damage that typically results from biochemical imbalances. Mice that genetically lack the ability to produce this enzyme develop ALS (Lou Gehrig's disease). We now know that cannabinoids protect against the development of this disease, however, they do not protect against the death associated with this illness [6], a dichotomy not yet understood.

A source of pain for many individuals involves trigeminal vascular neurons, which are thought to be involved with initiating migraine headaches. Ackerman et al [7] conclude "*CB receptors may have therapeutic potential in migraine, cluster headache or other primary headaches, although the potential hazards of psychoactive side-effects that accompany cannabinoid treatments may be complex to overcome.*" This type of strange commentary is pervasive in the scientific literature. The default perspective found in the scientific literature is that one should endure pain and suffering rather than bare the terrible psychological effects of cannabis consumption. The mind-altering properties of narcotic pain-killers, antidepressants, tranquilizers and sleep medications are okay, just stay away from the killer weed. Despite ongoing governmental malfeasance, additional research examining the role of the cannabinoid system and migraine headaches suggests a relationship between the headaches and an endocannabinoid deficiency [8].

With cannabinoids intimately involved with so many biological processes, what other diseases might be associated with cannabinoid deficiencies? Both anecdotally and experimentally, cannabinoids seem to benefit those suffering from multiple sclerosis. In one study, the synthetic cannabinoid Nabilone was shown to significantly reduce

spasticity-related pain [9]. In another study with multiple sclerosis patients, cannabinoids decreased the frequency of urination [10]. In a commentary on a newly published article [11] Raphael Mechoulam, the father of cannabinoids chemistry, writes that multiple sclerosis may disrupt the endocannabinoid protection mechanism [12].

## CARDIOVASCULAR SYSTEM

A general theme of cannabinoid activity is inhibition of inflammation and related free radical damage. In the immune system, cannabinoids regulate the balance between free radical production and their inhibition [13]. Inflammation and free radical production are important defense mechanisms used by the immune system to fight infectious invaders. The immune system regulates the level of inflammation in the circulatory system. A chronic pro-inflammatory response is a prime determinant in the development of arteriosclerosis, and can be reversed by cannabinoids in mice [14]. Unfortunately, the comparable experiment in humans has not yet been done. However, mice often serve as a good model for human immunology.

## SKELETAL SYSTEM

The global homeostatic role of the endocannabinoid system is again demonstrated by their control of the skeletal system. Earlier publications lead to some confusion in that some data indicated that cannabinoids might promote osteoporosis, whereas others suggested the opposite. Experiments published in 2006 provided new insights into the regulation of bone mass by the endocannabinoid system. Mice that have had their CB2 receptor genetically "knocked out," develop age associated loss of bone mass, a condition that appears similar to osteoporosis in humans [15]. Thus, CB2 simulation appears to prevent bone loss. Similar results were found with CB1 knock out mice [16].

## CONSCIOUSNESS

Many people use and enjoy marijuana because of the effects that it has on one’s consciousness. The year 2006 has produced some interesting new science in this area, in general, supporting the anti-depressive effects of cannabis. A study by Parish and Nicols [17] showed that stimulation of the serotonin receptor (5-HT2a) produced the endocannabinoid 2-arachidonylglycerol. The obvious question is how much of the antidepressive effects produced by serotonin uptake inhibitors is due to the production of endocannabinoids? Similarly, another study demonstrated that cannabinoids reduce anxiety by stimulating another class of serotonin receptors (5-HT1a) [18].

## BEATING AROUND THE BUSH

The possibility of increasing the levels of endocannabinoids by decreasing their rate of breakdown is an exciting new area of drug development. In agreement with earlier findings [19], elevating anandamide levels by inhibiting FAAH with an inhibitor "elicits significant, anxiolytic-like, antidepressant-like and analgesic effects" [20]. These findings, of course, provide unmentioned support for the use of cannabis for these same

conditions.
We know that elevating endocannabinoid levels has affects that are similar to consuming THC [21].

## CANCER

Cancer is one of the most exciting areas under investigation for the therapeutic application of cannabinoids. For many years the anti-nausea properties of cannabinoids was thought to be the primary use of cannabis for cancer therapy. Over the past few years, the greater potential for cannabinoids in the treatment of cancer has been revealed. Cannabinoids have been demonstrated to kill the variety of tumor cells, as well as to inhibit activities associated with metastasis (spreading) [22]. During this past year THC was shown to inhibit the replication of breast cancer cells [23]. Activation of cannabinoid receptors decreased tumor growth, angiogenesis (formation of new blood vessels necessary for tumors to grow) and metastasis, while increasing apoptosis (cell death) of melanomas in mice [24]. Additionally, cannabinoids were found to kill pancreatic cancer cells [25]. In 2006, the world had its first pilot human clinical trial of THC for cancer treatment [26]. This study was too small for proper statistical analysis, however, it seems that the drug was safe and inhibited tumor growth albeit temporally.
Since cannabis is frequently used by cancer patients to relieve nausea, lack of appetite, depression, and difficulty sleeping [27], a concern has been its possible effect on chemotherapeutic drug sensitivity. A recent study demonstrated that a variety of plant derived cannabinoids inhibited a protein that pumps therapeutic drugs out of cancer cells and is typically associated with drug resistance [28], thus providing another possible significant benefit to cancer patients who consume cannabis.
Since smoking is the most widely used route of cannabis administration, a long-term concern has been its possible carcinogenic effects. A recent epidemiological study demonstrated that cannabis smoking does not seem to cause cancers of the respiratory tract [29], confirming my earlier prediction [30].

## DANGERS OF CANNABIS USE

All humans suffer from a common biochemical imbalance. We are all aging, and aging is believed to be a consequence of accumulated free radical damage. With respect to the biochemistry of aging, cannabinoids appear to be beneficial. They not only appear to inhibit age related illnesses such as multiple sclerosis [31] and diabetes [32], but their absence increases the probability of premature death [33]. However, with respect to the body’s method of defense against certain infectious diseases, an excess of cannabinoids could be harmful or even lethal, in particular, when fighting intracellular parasites such as those responsible for Legionella disease [34] and tuberculosis [35].
Another possible danger that may result from cannabis consumption involves the liver. On the one hand, recent data shows that hepatitis C patients who consume cannabis are more likely to successfully complete there treatment regime [36]. On the other hand, turning off the CB1 receptors may be beneficial for treatment of liver fibrosis [37] since CB1 activation seems to be involved in this pathology [38].

## CONCLUSION

In the marijuana plant, nature has provided us with a well-stocked medicinal chemistry set. Everyday new peer reviewed scientific publications support and extend the benefits that this plant can provide mankind. When you couple the scientific data with the observations of medical marijuana users, the support for medical marijuana use is overwhelming. How then is it possible that there remains resistance to the medicinal use of marijuana? A possible answer may be found in the simple truth that in any population of people there will be those who are cannabinoid endowed and others who are cannabinoid deficient. When the deficiency involves the areas of the brain that allow us to change our minds and replace out dated information with new information, change becomes difficult. These individuals unfortunately lack some of the necessary cannabinoid-based biochemistry. This scenario raises the question: are cannabinoid deficient people selected for by our political process? [1]

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