Endocannabinoids: Marijuana from Within
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INTRODUCTION

Marijuana has been used medicinally for thousands of years, having been documented in the world's first pharmacopeia, written around 2700 BC in China, as well as on clay tablets from the ancient Assyrians [1]. Historically, cannabis preparations have been used to treat a wide variety of illnesses, including: pain, seizures, spasticity, and cholera. Today thousands of peer-reviewed articles, from researchers around the world, explain the underlying science responsible for the many biological activities of the plant. Not surprisingly, plant derived cannabinoids uniquely mimic the recently discovered endocannabinoid system (marijuana from within). Endocannabinoids are an exploding topic of research. As a result, this chapter will examine only bits of the huge database of new scientific knowledge, specifically those that exemplify the endocannabinoid connection with underlying physical principles of the physics of life.

All body systems, and the components from which they are made, are functionally regulated in a manner analogous to how a thermostat maintains temperature in a building, they must be turned on and off appropriately to maintain dynamic stability, i.e. balanced flow, heat gain and heat loss. Dynamic balance is a fundamental property of living systems. In contrast, a penny lying on a table or balanced on its side is stable in the absence of any flowing quantity such as energy. In biological systems, enzymes made from proteins are ultimately responsible for the synthesis of ligands. These are chemical compounds that bind to receptors, also proteins, serve as switches for initiating biochemical responses to biochemical signals that often reflect the status of a cell with respect to its environment. Biochemical signals must also be turned off, therefore, other appropriately controlled enzymes must be available, which can break down the original initiating signals, or turn off the response to them. This biochemical-balancing act is known as homeostasis. It occurs at all levels of life: within cells and between cells, within organs and between organs, on up the scale to include individuals with their environment, and their societies. What is amazing, and not commonly known, is that dynamic steady states naturally result from flowing energy and matter, they self-organize. In other words, the thermostat makes sets itself (mathematically, there is an attractor)

The sum of an individual's homeostatic activities is represented by one's health. It is now known that the endocannabinoid system is an all-pervasive modulator of biochemistry. Basic principles of modern physics can provide a scientific foundation that explains life's physical operational mechanisms, and the important role that the endocannabinoid system plays in maintaining them. Based on far from equilibrium thermodynamic principles, characterized by emergent behavior (new forms of organization that cannot be directly mapped to their causes in a linear mechanistic manner, such as self-assembling enzymatic circuits), the endocannabinoid system regulates biochemical flow across many scales of organization. An as yet largely unstudied area concerns the impact of various endocannabinoids on society. The prevalence of these physical processes in the real world suggests that consciousness itself is an emergent phenomenon that is critically regulated by the endocannabinoid system. Following this line of thinking, it appears that the

endocannabinoid system may participate the mind/body connection, perhaps even regulating the placebo effect, were the mind appears to directly control health.

WHAT ARE ENDOCANNABINOIDS?

Endocannabinoids are a group of lipid compounds (fat-like) that are produced by some invertebrates [2] and all vertebrates including humans . Their classification [4] is based on their biological activity, which is often similar to that of the main psychoactive phytocannabinoid (plant cannabinoid) delta-9 tetrahydrocanabinol (THC) found in the marijuana plant.

The first endocannabinoid discovered was, arachidonyl ethanolamine, and was named anandamide (ananda is Sanskrit for bliss, hence the blissful amide) . Subsequently, 2-arachidonoyl glycerol was isolated from canine gut and identified as a second endocannabinoid . Both of these chemicals are ultimately made from essential fatty acids such as are found in fish and seed oils [9]. An as yet unanswered question is how much of the health benefits attributed to essential fatty acids such as omega 3's are due to their products, endocannabinoids (see section on cardio-protection below)? When cannabinoid receptors are activated, various biochemical properties in cells are altered, as is communication with other cells. The Pandora's Box of endocannabinoids and their modes of action has been opened. Today a number of additional endocannabinoids have been reported and their possible therapeutic applications are under investigation .

AEA and 2-AG are the most studied, and most abundant, endocannabinoids. However, numerous other related molecules also appear to be, or to have, related endocannabinoid-like activity, including N-arachidonoylglycine , stearoylethanolamide , N-arachidonoyldopamine , homo-g-linolenylethanolamide and 7,10,13,16-docosatetraenylethanolamid virodhamine , and noladin ether .

Some molecules indirectly promote endocannabinoid activity [20], for example, instead of acting directly on cannabinoid receptors they inhibit the activity of enzymes that breakdown endocannabinoids thus effectively increasing the activity of existing endocannabinoids, the entourage effect . New compounds that inhibit endocannabinoid breakdown are under development for therapeutic application. For example, URB597 is under study as a treatment for nausea , as a treatment for emotional disorders such as depression , and to promote vasodilation .

Endocannabinoids are typically synthesized on demand in a calcium dependant manner by hydrolysis of phospholipid precursors . However, despite decades of effort, the biosynthetic pathways for endocannabinoid biosysnthesis are not firmly established . A novel pathway for the synthesis of anandamide has recently been published [29]. Their catabolic metabolism by cyclooxygenase 2 (COX2) [30] yields a novel class of bioactive lipids known as prostamides . Prostamides are chemically similar to prostagandins, however they have a longer lifespan in the serum [32]. Typically they mediate anti-inflammatory events that help to balance the pro-inflammatory effects of many prostaglandins. Pharmaceutical companies have developed COX2 inhibitors to turn off the pro-inflammatory action of prostaglandins. However, these drugs also turn off the production of cardio-protective prostamideswhich has resulted in thousands of deaths.

Hence, while endocannabinoids are often produced for local action, their metabolic products can have wide spread activities, often affect global homeostasis.

HOW DO ENDOCANNABINOIDS FUNCTION?

Amazingly, endocannabinoids regulate all body systems including cardiovascular, digestive, endocrine, excretory, immunological, nervous, musculo-skeletal, respiratory, reproductive, tegumentary (skin) where they often exert health-promoting properties [34]. The first modern scientific proof of the endocannabinoid system came with the discovery that a potent radioactive analogue of THC uniquely bound to specific areas in the brain, hence suggesting the presence of a THC receptor . Soon after the receptor was discovered in the nervous system (CB1 receptor), it was cloned and found to belong to the large family of G-coupled protein receptors (GCPR) . A few years later a second receptor was cloned from immunological cells (CB2 receptor) . The CB2 receptor is 44% homologous to the CB1 receptor , and since it was found outside the central nervous system, it became known as the peripheral receptor. Ongoing cannabinoid research suggested the existence of additional endocannabinoid receptors. A recent patent application by a pharmaceutical company identified GPR55 as a new cannabinoid receptor . The CB1, CB2 and GPR55 receptors are typically found on the cell surface, but their local lipid environment and internalization affect their functionality .

Endocannabinoid biochemical circuitry is extremely complicated since endocannabinoids also bind other important receptors and channels either directly, or after enzymatic processing. For example, AEA is also an endovanilloid that acts on vanilloid (TRVP1) receptors . TRVP1 channels are non-selective cation channels that belong to the TRP family of proteins. They are found not only on nerve cells, but also on a variety of other cell types . TRVP1 receptors regulate pain and are responsive to heat, acid and pressure . The complexity of cannabinoids and their closely related circuitry is again apparent. Recent work shows that AEA inhibits 2-AG synthesis by activating TRVP1 receptors . Additionally, AEA on the one hand promotes lipogenesis by activating CB1 receptors, while on the other hand it inhibits lipogenesis through TRVP1 receptors . Also, TRPA1 channels, which are responsible for deep cooling activated pain are inhibited by TRVP1 activation through activation by cannabinoids . The complexity of endocannabinoid action is further underscored by the fact that the often have biphasic affects, meaning a particular response is elicited at a low dose, and the opposite affect may result from a high dose .

The regulation of lipid metabolism is a common denominator for much cannabinoid and related molecular activities. Peroxisome Proliferator Activated Receptors (PPARs) are regulators of lipid metabolism. PPAR alpha and delta promote lipid oxidation , whereas PPAR gamma promotes lipogenesis . Cannabinoids activate peroxisome PPAR alpha and PPAR delta thus increasing fat burning. They also activate PPAR gamma [53] receptors that increase fat deposition. Thus, endocannabinoids promote both fat deposition and fat oxidation. Which process dominates and under what conditions is not yet fully understood; yet genetics is certain to play a crucial role in this balancing act.

Endocannabinoids also regulate serotonin action through their effects on the 5-HT receptors , opiod receptors , nicotinic acetylcholine receptors , glycine receptors, and

sodium, potassium and calcium channels [57]. Together, these interwoven biochemical circuits control a significant number biochemical processes up to and including consciousness. Thus, varying levels of cannabinoid activity in a population must have social consequences[58].

Presently, it is not known if the spectrum of cannabinoid activities found in the different sub species of cannabis (*Cannabis sativa, indica, and ruderalis*), as well as the differences in the biological activities of different cultivars [59] encompass the various biological properties of endocannabinoids. The varying chemical profiles found in different strains of cannabis may explain strain-specific therapeutic benefits claimed by medical marijuana patients. Currently, an little explored possibility is that strain differences may reflect an individual's need to supplement specific endocannabinoid deficiencies that characterize specific illnesses [60].

As a result of the complexity exhibited the endocannabinoid system, many aspects of biology must be integrated when trying to develop a comprehensive understanding of the endocannabinoid system's biological properties. It is therefore interesting to consider that emergent behavior must be a natural phenomenon intrinsic to the endocannabinoid system. Thus, while a reductionism approach provides tremendous details regarding the specifics of endocannabinoid biochemistry, this perspective cannot predict the higher levels of organization and complexity that are non-linearly related to their underlying causes emergent behavior. The perspective guiding this chapter is that health and consciousness of an individual are emergent phenomena. Hence we must look at both the details and the big picture in order to appreciate the unique therapeutic benefits associated with manipulating the endocannabinoid system.

THE PHYSICS OF LIFE

In order understand the great complexity of the endocannabinoid system, and its central role in human health, it must be viewed from a scientific framework that specifically deals with complexity. Sans details, the common thread running through this chapter is the integration of modern endocannabinoid science with the physics that provides a scientific perspective of what life is. Simplistically, when energy flows through large collections of molecules, they acquire a creative quality that results in dynamic self-organization, a phenomenon that is thought to be responsible for life and the evolutionary process [61] [62] Using physical and biochemical concepts as a foundation, life/death, health/illness, and social, political and economic principles can be examined from underlying physics, and how, at all levels, these processes are uniquely regulated by the endocannabinoid system [58].

CREATIVE ENERGY FLOW AND LIFE

In order to appreciate the medical opportunities provided by manipulating the endocannabinoid system, we must consider the basic properties of life itself.
For the first time in mankind's history, we can look at life from a truly scientific prospective, using tools that will enable us to understand its basic properties. The details of the physics of life will not be examined, but 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 work). In other words, equilibrium is the opposite of life. Thermodynamics refers to the flow of energy. 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 promoting or regaining one's health and increasing one's organization and energy flow. An example is physical training, where changes occur that span biochemical to behavioral levels. Similarly, learning and enhanced thinking skills (including one's state of mind) also represent movement from equilibrium. Again, our endocannabinoid system is a master regulator of each of these processes. With such wide-ranging, multi-scaled regulatory activities, the endocannabinoid system is likely to play an important role in connecting the mind and body.

A basic far from equilibrium characteristic is that of dynamic balances. An additional on is that when there is enhanced energy/mass flow through as system of balanced opposing forces, stable steady state can undergo a dramatic shift over a short period of time and can result in cyclic and chaotic behaviors. The consequences of these non-linear rearrangements (phase changes) can be dramatic. For example, endocannabinoids are known to regulate the balance of open/closed-mindedness (the ability to learn new things and replace the old), depression/euphoria, stress/reduced stress, pain/reduced pain, hunger/satiety. Think of the impact that these macroscopic biological activities have on an organism's interaction with its environment, and that they all emerge from organized underlying biochemical phenomena.

LIFE AND EVOLUTION ARE A SERIES EMERGENT PHENOMENA

Regulated energy and mass flow keeps life away from equilibrium. The movement towards equilibrium is characterized by aging, illness and death. On community, species, individual, cellular and sub-cellular levels, living systems maintain the critical flow of organizing energy by extracting it from their environment, and by dumping their waste products back into the environment. Endocannabinoids play crucial roles in each of these processes.

In addition to distance from equilibrium, in fact a result of it, another fundamental characteristic of living systems is that the whole is greater than the sum of its parts (emergent behavior). Pieces of a system work together and create something new and different, something that would not have been predicted by observing the individual components in isolation. How do these phenomenon impact on the health of cells, individuals, communities and society, and what role is played by the endocannabinoid system? Are consciousness and health emergent phenomenon, with the endocannabinoid system being a critical player in the emergence process? Are endocannabinoids critical components of the mind-body link, and is the endocannabinoid system involved with the placebo affect?

ENDOCANNABINOIDS: PRO-LIFE ANTI-AGING MOLECULES

Before considering the role of endocannabinoids in the aging process, we should consider what aging is. As mentioned above, life is intrinsically a far from equilibrium phenomenon [62,63]. Hence we can equate health with an organism's distance from equilibrium, and both aging and age-related illnesses as an organism's movement towards equilibrium. Again, equilibrium is when disorder is maximized. From this perspective, the role that cannabinoids play in the aging process can be restated as how do cannabinoids impede and organism's movement towards equilibrium, and what are biochemical events responsible for the movement towards equilibrium?

It is generally accepted that free radicals are critical contributors to the aging process [64]. Free radicals are highly reactive compounds that react with all biologically important molecules including carbohydrates, lipids, nucleic acids (RNA and DNA), and proteins, as well as their building blocks. Mitochondria, specialized energy producing organelles of eukaryiotic cells, are responsible for producing most free radicals . This line of thinking has progressed from viewing proteins as the critical targets, to viewing nucleic acids, in particular DNA, as the critical target, to taking a more systematic view from which all the biological components must work together in an harmonious, integrated fashion, and thus they are all critical targets. Thus the question becomes, can cannabinoids, both endo and exo, impact on the biological consequences of free radicals? Two important studies address this question without examining the specific mechanisms.
The first hint that activating the endocannabinoid system might have anti-aging properties came from a study done within the NIH itself in which after 2 years of THC administration to rodents, "Survival of all dosed groups was generally significantly greater than that of the controls". In contrast, when the ability of a mouse strain to produce the CB1 receptor was genetically "knocked out", the mice died significantly younger .

The anti-aging properties of cannabinoids could result from their direct capacity to scavenge free radicals , or from their impact on free radical generating, proinflamatory metabolic pathways . In essence, free radical damage to living systems can be considered to be biological rust [72], whereas endo and exo cannabinoids are the oil of life that reduces biochemical friction [34].

ALL BODY SYSTEMS ARE REGULATED BY ENDOCANNABINOIDS
As the multi-cellular complexity of life evolved, new structures were necessary to support the enhanced dialog between an organism and it's environment. A primary requirement would be the development of a more organized capacity for greater energy/mass through put, in other words the development of the digestive system. A reliance on simple diffusion for nutrient and waste transfer would limit the far from equilibrium driven mandate for the biosphere to increase entropy production to the environment. Thus, the concerted evolution of a digestive system, sensory organs and the nervous system, would in a concerted manner drive the evolution of the musculoskeletal system, which, as organisms evolved enhanced mobility, would require the protective properties of the evolving immune system. All these biological components work together and mutually enable each other so that an organism can sense it's environment, determine it's thermodynamic compatibility with it, and make the necessary adjustments in an attempt to optimize its place in the unfolding universe. Surprisingly, as these body systems synergistically evolved, endocannabinoids became crucial modulators of the multi-dimensional biochemical balancing strategies that characterize living systems. Some representative examples are found below.

THE DIGESTIVE SYSTEM
From a far from equilibrium perspective, in order for a system of molecules to undergo a nonlinear rearrangement that will increase its complexity, there must be an excess of potential for increased mass and energy flow. Thus, this rule should have driven the evolution of single celled organisms into more complex multi-cellular forms. Hence the first level of complexity that must have been selected for was the capacity to more efficiently intake food and removal wastes. In fact it appears that around the same time that this evolutionary step first occurred, some 600 million years ago, the primitive

beginnings of the endocannabinoid system first appeared [73]. Today it is obvious that the endocannabinoid system evolved into a fundamental regulator of hunger and the digestive/excretory system [74].

Endocannabinoids regulate many aspects of food acquisition, and processing from one end of our digestive tract to the other. The profound effect that cannabinoids have on eating is well known. The "munchies" result from cannabis consumption because THC mimics the release of endocannabinoids in the brain's appetite center that results the mental feeling of hunger . Endocannabinoids stimulate hunger both in the brain [76] and in the gut . An interesting holistic behavioral affect of endocannabinoids is seen in the regulation of song in adult male zebra finch, where courtship, kin recognition, and nest defense are components of mating behavior . When these birds have limited food availability, or are treated with cannabinoids, the transcription of genes involved in the auditory processing of songs is inhibited. Hence endocannabinoids are participating in the integrated regulation of feeding, reproductive behavior, and aggression.

Dramatically, the significance of endocannabinoid signaling in feeding behavior is underscored by the feeding new born mice a CB1 antagonist (SR141716A, also known as Rimonabant), they die . Since Rimonabant's (and other CB1 antagonists) inhibit feeding, it has been developed as a treatment for obesity . It has undergone clinical trials in Europe and the USA. Today it is a commercial product in Europe for weight control, however it failed to pass the FDA approval process and remain unavailable in the United States. When the multi-facetted involvement of the endocannabinoid system in maintaining homeostasis in living systems is considered, turning of the CB1 receptor seems to be a dangerous undertaking. In fact, Rimonanant-induced nausea and depression are common reasons for patients discontinued its use during the clinical trials . Futhermore, in support of the neuroprotective properties of cannabinoids (see section below on the nervous system), a patient, using Rimonabant for obesity, developed multiple sclerosis .

The age related accumulation of free radical damages is at least participatory in the etiology of age related illnesses of the digestive tract, as a result, both a scientific studies and anecdotal observation are in agreement. For example, anecdotal observations suggest that cannabinoids are beneficial for treating gastro-intestinal reflux disease, a condition where stomach acid erodes the esophageal wall as a result of the esophageal sphincter failing to fully close. The sphincter closes when it is relaxed, and this process is promoted by endocannabinoids acting on CB1 receptors in the dorsal vagal nerve complex as demonstrated in ferrets.. Another important gastric disorder is ulcers. The main cause of peptic ulcers is now known to be infection with H. pylori, which results in a strong pro-inflammatory Th1 cytokine response [84], and excessive acid production. Since endocannabinoids turn down the Th1 response, and inhibit acid secretion [85], it makes sense that cannabinoids have anti-peptic ulcer activities .

By similar mechanisms of immune cytokine modulation and regulation of neurological activity, endocannabinoids have protective roles in the lower gastrointestinal tract where they protect against colonic inflammation . The latest data indicates that the protective actions of endocannabinoids in the lower gastrointestinal tract is not simply the result of CB1 activity, but also involves TRPV1 and CB2 receptors [88]. Interestingly, the latest

research indicates that the CB2 are up-regulated during pathology independent of tissue type.

THE NERVOUS SYSEM

Endocannabinoids are central players in the nervous system, both centrally and peripherally. The CB1 receptor is the most abundant G-coupled protein receptor in the brain [89]. When involved in nerve transmission, endocannabinoids are released by postsynaptic neurons and travel retrograde across the synaptic cleft and where they bind to specific receptors . Alternatively, they may be transported [91] into cells for degradation by specific enzymes such as fatty acid amino hydrolase and monoacylglycerol lipase .

Endocannabinoids provide important protection for the nervous system, since free radicals again play an important role in nervous system pathologies including ALS , Huntington's Disease , Alzheimer's Disease [97]. The detrimental consequences of excessive neurological stimulation as induced by excitotoxins and epileptic seizure , inflammation , as results from traumatic brain injury , stroke and infections, are all reduced by endocannabinoids. However, again demonstrating the critical importance of appropriately balanced biochemical circuits, and the at times contradictory properties of the endocannabinoid system, COX metabolites of the endogenous cannabinoid 2-AG promotes excitatory glutaminergic transmission and associated nerve injury and death .

The negative consequences that marijuana has on memory commonly know, and well documented . The important question that arises from these observations is "what is the biological role of the endocannabinoid system with respect to memory?" Possible answers will be examined from a holistic perspective. A healthy individual must have an appropriate balance of remembering and forgetting, imagine if all the things you would rather forget dominated your thoughts. Post-traumatic stress and depression are natural consequences in humans who could not forget unpleasant memories. Again, nature has selected the endocannabinoid system as a critical modulator of balancing remembering and forgetting.

A poignant example that demonstrates consequences of insufficient forgetting comes from behavioral studies with CB1 knockout mice . While both wildtype (normal) mice and knock out mice were able to learn the solution to a water maze (finding a platform to get out of the water), the CB1 deficient knockouts could not relearn the solution when the platform was moved to a new position [102]. If cannabinoids regulate similar neurological processes in humans, it is inevitable that this form of relearning will vary in any population with people having abilities above and below the average. The human equivalent of the relearning behavior of mice might be open-mindedness, a quality anecdotally described as enhanced by the use of cannabis. If this analysis is correct, endocannabinoid activity regarding this phenotype could have important implications for the survival of mankind, where open mindedness may be necessary to change human behavior to minimize the consequences of the rapidly changing environment that results from human activities [58].

The Immune System

The function of the immune system is simple, to protect an individual from danger. However the mechanisms by which the immune system functions to accomplish this task are incredibly complicated and far-reaching in that they impact on the biochemistry of all

other biological systems. The far from equilibrium thermodynamic model of life is based on a multidimensional web of biochemical balance that has pro- and anti- inflammatory processes as a core component. The immune system is a critical regulator of this core. The immune system responds to environmental perturbations impinging on an organism. Free radical production is a universal signal of imbalance between an organism and its environment. However, organisms have evolved the capacity to respond by producing and using free radicals and other reactive oxygen (ROS) and nitrogen (RON) chemicals as sanitizing agents to fight infection. This response, however, must be kept in check due to the highly reactive nature of these chemical species. By modifying DNA, RNA, proteins and lipids, free radicals reduce an organism's distance from equilibrium by reducing the efficiency of biochemical flow (the friction of life). The endocannabinoid system critically tries to restore balance by reducing the inflammatory response and promoting the anti-inflammatory response. The health consequences of pro-inflammatory imbalances are all pervasive.

Most immune disorders can be attributed to a pro-inflammatory imbalance that results in the immune system attacking inappropriate targets that results in autoimmune disease. Arthritis , Crohn's Disease [104], diabetes [105], Lupus , and multiple sclerosis all have proinflammatory imbalances that results in tissue destruction. Each of these illnesses is, in part, characterized by excessive pro-inflammatory cytokines (Th1 response), which are protein messengers through which the immune system communicates with itself and the rest of the body. Since the endocannabinoids are important regulators of the Th1 versus the anti-inflammatory Th2 response [108], as well as the development of the immune system itself, some of these illnesses are now being characterized as endocannabinoid deficiencies including melancholic depression [109], multiple scherosis [110], migraines .

CARDIOVASCULAR SYSTEM

Inadequate attempts by the body to use endocannabinoids to mediate protection of the cardiovascular system may be seen in a variety of pathologies. As a result, many illnesses may be characterized by endocannabinoid deficiencies. Excessive pro-inflammatory activity has a profound impact on cardiovascular health. For example, pro-inflammatory TH1 cytokines inhibit the burning of fat by macrophage, which in turn promotes their conversion to fat laden foam cells. Additionally, the Th1 cytokine profile promotes macrophage migration through the walls of blood vessels, where some die and turn into the plaque that results in atherosclerosis, "hardening of the arteries." Recent work in mice demonstrates that cannabinoids can reverse this process by activating the CB2 receptors .

Additionally, when a cardiac blood vessel blockage is created in mouse models, endocannabinoids acting through the CB2 receptors, protect the heart muscle from the damage that results from oxygen deprivation, as well as when reperfusion replenishes the oxygen supply and generated free radicals . It now appears that remote ischemic preconditioning, when damage at one site protects other sites, occurs through a CB2 mechanism In addition to these protective properties, endocannabinoids, in animal models endocannabinoids also regulate cardiac [115], mesenteric , kidney and cerebral circulation Wagner et al., 2001, Eur J Pharmacol, 423, 203-10} by promoting vasodilation.

It should be noted that while cardiovascular pathologies most seem result from an excessive pro-inflammatory response, there are others that seem to result from an

excessive anti-inflammatory/TH2 response. For example, the cardiac contractile dysfunction that is associated with liver cirrhosis is mediated by the CB1 receptors , as is the low blood pressure associated with hemorrhagic shock .

PAIN MANAGEMENT

Societal open mindedness, or the lack there of, has important health ramifications when considering pain management especially for cancer patients (see below). The combination of cannabinoids with opiates for pain treatment provides unique benefits in that a positive analgesic synergy has been found between these two drugs . Furthermore, this combined treatment reduces the tolerance that normally develops to opiates . When one considers that pain is often associated with inflammation and tissue degradation as is found with arthritis, cannabinoids become an ideal tool to assist with chronic pain management in that they reduce both inflammation and the associated degradation [122].

CANCER

The importance of modulating the endocannabinoid system for pain management is underscored with cancer. The use of narcotics, aside from their impact on the quality of life, seems to enhance biological responses that promote tumor metastasis [123]. In contrast cannabinoids inhibit metastatic mediators like epithelial growth factor VEGF , adhesion and migration , while also having anti-nausea and anti-depressive activities , although there is also evidence to the contrary . The numerous benefits that cannabinoids can offer cancer patients are underscored by the direct cancer killing properties of cannabinoids. In the 1970's it was already known that cannabinoids could kill Lewis lung carcinoma cells . We now know that cannabinoids (endo, phyto and synthetics) halt the growth or kill many different types of cancers including glioma, skin cancer , , breast cancer , prostate cancer , lymphoma , , melanoma .

CONCLUSION

This chapter has provided a limited, but holistic overview of the complexity of the endocannabinoid system and its involvement in maintaining healthful homeostasis. We have not covered important areas such as the involvement of endocannabinoids in regulating the skeletal system, the reproductive system, addictive behaviors etc. The field of endocannabinoid research is logarithmically expanding since endocannabinoids regulate an incredibly diverse array of biochemical events that transcend sub-cellular to societal scales. As such, the endocannabinoid system exemplifies the profound creative nature of the physics of life, far from equilibrium thermodynamics, by participating in holistic biochemical behavior that ideally manifests as health. Endocannabinoids, through multiple modes of action, are critical regulators of energy balance [139], and energy flow is essential in maintaining organization of flow dependant structures that result from distance from equilibrium. From a far from equilibrium perspective, the multifaceted implications of this regulation can be unique to each person as determined by limit cycles, where mass and energy flow result is self-assembling regulatory circuits [140]. Hence imbalances characterized by an over active, or under active, endocannabinoid system are functions of the individual (genetics and environmental history) and the tissue or organ under consideration. Typically, since we are all aging, most endocannabinoid imbalances are of insufficiency. Endocannabinoids are unique tools that can help shift biochemical imbalances (inappropriate limit cycles), not by pushing change in isolated areas, but by initiating change through many interrelated components of biochemistry. A movement towards a more healthy state results from establishing new limit cycles driven

by energy acquisition that leads to novel multi-scaled communication and cooperation. Our cells, our bodies, our societies are all profoundly impacted by endocannabinoids.

Endocannabinoids have unknowingly been manipulated in an effort to improve health and relieve suffering for decades. The commonly used analgesic, acetaminophen, is metabolized to produce an inhibitor of anandamide transport (AM404), thus effectively raising endocannabinoid levels . The commonly used general anesthetic propofol also inhibits FAAH . Are the anti depressive effect of electro shock therapy due to elevated endocannabinoid levels elicited to protect the brain? Osteopathic manipulation raises anandamide levels 168% . Yogurt induces CB2 levels in the gut . Activities as simple as taking a warm bath to relieve stress and pain are likely to increase endocannabinoid levels since through their action in the hypothalmus they can reduce an elevated body temperature [145].

A person's life is the progressive unfolding of the interactions of the biological system with its environment. Consciousness has defined possibilities for examining and attempting to control this process. An individual can look backward to what has already happened, look forward to what is projected to happen, or a person can be present and can experience the now. The latter two possibilities are promoted by cannabinoids as a consequence of how cannabinoids typically have a negative impact on memory but favor relearning and novely, thus potentially fostering the anecdotally noted enhancement of creativity by exocannabinoids. Cannabinoid research has come a long way in a relatively short period of time, where it will go remains to be seen, but it certainly appears manipulating the endocannabinoid system will have an expanding role in the future of mankind.

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