Endocannabinoids: Multi-scaled, Global Homeostatic Regulators of Cells and Society

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Living systems are far from equilibrium open systems that exhibit many scales of emergent behavior. They may be abstractly viewed as a complex weave of dissipative structures that maintain organization by passing electrons from reduced hydrocarbons to oxygen. Free radicals are unavoidable byproducts of biological electron flow. Due to their highly reactive chemical properties, free radicals modify all classes of biological molecules (carbohydrates, lipids, nucleic acids, and proteins). As a result, free radicals are destructive. The generally disruptive nature of free radicals makes them the "friction of life". As such, they are believed to be the etiological agents behind age related illnesses such as cardiovascular, immunological, and neurological diseases, cancer, and ageing itself.

Free radicals also play a critical constructive role in living systems. From a thermodynamic perspective, life can only exist if a living system takes in sufficient negative entropy from its environment to overcome the obligatory increase in entropy that would result if the system could not appropriately exchange mass, energy and information with its environment. Free radicals are generated in response to perturbations in the relationship between a living system and its environment. However, evolution has selected for biological response systems to free radicals so that the cellular biochemistry can adapt environmental perturbations by modifying cellular gene expression and biochemistry.

Endocannabinoids are marijuana-like compounds that have their origins hundreds of millions of years in the evolutionary past. They serve as fundamental modulators of energy homeostasis in many multi-cellular organisms including all vertebrates. They have widespread biological activities that may often be attributed to their ability to minimize the negative consequences of free radicals. In fact, since cannabinoids (endo and exo) possess many anti-aging properties, they may be viewed as the "oil of life".

The biological effects of cannabinoids transcend many scales of organization. Cannabinoids regulate sub-cellular biochemistry, intercellular communication, and all body systems (cardiovascular, digestive, endocrine, immunological, nervous, musculo-skeletal, reproductive, respiratory, and tegumentary). It is proposed that their emergent properties extend to social, political, and economic phenomena. As a result of man's unprecedented impact on his surroundings, the selective pressure on the evolutionary progression of man's endocannabinoid system has novel time constraints that may be best met by behavioral modification. Presently, mankind is engaged in an evolutionary battle between more primitive members of a relatively cannabinoid deficient population and those relatively more endowed. The outcome of this genetic conflict may determine man's survival.

1. Introduction

The intent of this paper is to integrate a far from equilibrium perspective of biology, from which emergent behavior is intrinsic, with the explosion of scientific investigations into the endocannabinoid system. Endocannabinoids are marijuana-like compounds [Devane et al., 1992] produced by all deuterosomes [McPartland et al., 2006]. They are believed to have their evolutionary origins 600 million years in the past. Over the past decade and a half, since the identification of cannabinoid receptors [Herkenham et al., 1990], research into the cannabinoid system has grown exponentially. Major international pharmaceutical

companies are engage in cannabinoid research, and products to turn on /off the system are in the pipeline.

2. Hypothesis

The endocannabinoid system is a global homeostatic regulator [Melamede, 2005]. The actions of the cannabinoid system transcend the scales of organization ranging from the sub-cellular within an organism to beyond an organisms boundary where it regulates extra-organismic, yet population dependant, hierarchal dissipative structures such as social, political, economic and religious systems. With such broad, multi-scaled activities, that have evolved over 600 millions years, the cannabinoid system may underlie evolutionary advanced phenomena. For example, it has been postulated that the endocannabinoid system may provide the mind body link that emerges as the placebo effect [Melamede, 2006]. Through their behavioral consequences, cannabinoids (and potentially behavioral biochemical regulators) create a hypervariable interface between an organism and its environment, thus linking behavior and evolution. Specifically, it is suggested that due to man's unprecedented impact on his environment, unique demands are placed on mans behavioral repertoire such that novel adaptive behavior is necessary man's survival.

3. Far From Equilibrium Thermodynamics

For many years life, characterized by high levels of organization, appeared to contradict the Second Law of Thermodynamics that states: entropy must always increase, and free energy must decrease. The concepts developed by Illya Prigogine describe how, as long as sufficient negative entropy flows into a far from equilibrium system, it can overcome the intrinsically positive entropy production of an isolated system [Kondepudi and Prigogine, 1998]. Thus entropy flow is necessary to maintain flow dependant (dissipative) structures such as living systems. The biosphere may be viewed as the grand dissipative structure of life with species and individuals as component dissipative structures contained within. Similarly, as the level of magnification increases body systems, tissues and subcellular components must have a successful far from equilibrium entropic balance.

$$dS_{T(total)}/dt = dS_{E(exchange)}/dt + dS_{I(internal)}/dt$$

Homeostasis is the process by which the inputs and outputs of entropy exchange flow to and from characteristic internal, flow dependent structures, essentially allowing them to constantly adapt to their constantly changing environment. The survival time of an individual/population is dependant on the rate of movement towards equilibrium as measured by illness and ultimately, death.

3.1 Energy Flow

As energy flows through a species three categories of possibilities regarding stability are evident:

1. a system may remain stable
2. the energy flow through a system might increase sufficiently to destabilize the system in which case:
    a. it may successfully bifurcate to a state of lower entropy (health and fitness).
    b. it may collapse to a state of higher entropy (apoptosis on a cellular scale, illness and death).
3. there may be insufficient energy flow through a system so that it collapses, either totally or to a lower, yet flow dependent, level of organization (apoptosis on a cellular scale, illness and death).

4. Endocannabinoid System

The cannabinoid system is composed of ligands, receptors and ligand transporting and degrading enzymes [Mackie and Stella, 2006]. Endocannabinoids are lipid metabolites that bind to the cannabis receptors (CB1 and CB2). CB1 receptors, originally thought to be mainly found in nervous tissue, have now been found in numerous other tissue types including skin, muscle etc. In contrast, the CB2 receptors are largely limited to cells of the immune system, but are also found in other tissues including the brain [Gong et al., 2006]. Cannabinoids are involved in the fundamental life, death, differentiation alternatives of cells [Guzman, 2005], and thereby extend through out the levels of biological organization.

4.1 Evolution

A far from equilibrium perspective of the evolutionary progression of living systems from single celled species to man may suggests successive bifurcations in which systems became more complex so that they can more efficiently generate external entropy [Melamede and]. Successful feeding behavior and the passage of waste products is an evolutionary prerequisite for the energy driven, ongoing, nonlinear rearrangements that characterize speciation. We now know that endocannabinoids are critical homeostatic regulators of all body systems, and perhaps most importantly of energy flow in general [Cota et al., 2003]. The activities of cannabinoids transcend scales from sub-cellular to organism. Thus, cannabinoids have the potential for their activities to become manifest as a whole that is greater than the sum of its parts. This concept becomes particularly applicable when one considers the impact of the cannabinoid system on the functioning of the brain [Fride, 2005].

Cannabinoids in the nervous system work via a novel retrograde synaptic mechanism [Wilson et al., 2001]. Endocannabinoids are synthesized and released on demand by the breakdown of membrane components in post-synaptic neurons. These lipid-like molecules defuse across the synaptic cleft where they stimulate receptors on pre-synaptic neurons where they are coupled to a variety of signal transduction pathways. The net result of cannabinoid activity is to protect neurons from potentially harmful excessive stimulation. This phenomenon occurs in many areas of the brain. In particular, there is a high density of CB1 receptors in the hippocampal region of the brain where memory and

learning are regulated. The effects of cannabinoids on these functions are far reaching, and have consequences that will be discussed below in the section on cannabinoids and behavior.

4.2 Cannabinoids and Behavior

The effects of cannabinoids on behavior are examined by stimulating receptors, inhibiting the receptors, or by genetically eliminating them. Additionally, there are receptor independent biochemical pathways that cannabinoids modulate. Behavioral studies performed with CB1 knockout mice provide important insights as to how these compounds function. Mice deficient in CB1 receptors initially learn better than their wild type counterparts [Bilkei-Gorzo et al., 2005]. However, as they get older, learning occurs more efficiently in the wildtype strain. This observation suggests that when memories are initially established, forgetting is not involved. However, as memories grow more complex and abstract thinking emerges, forgetting old knowledge becomes an important part of setting down new knowledge.

Experiments using a Morris water maze demonstrate the critical role that cannabinoids play in relearning [Varvel and Lichtman, 2002]. While type and CB1 knockout mice both learn how to solve the maze since that is how the kid out of the water. However if the position of their platform is moved the wildtype mice readily learn to go to the new position, whereas the CB1 knockout mice continue to return to the place that no longer has the escaped platform. The ability of cannabinoids to regulate relearning has important far reaching consequences that will be discussed below in the section on politics.

CB1 knockout mice further indicate the behavioral activity of the cannabinoid system [Zimmer et al., 1999]. Aside from increase mortality, these mice exhibit a number of behavioral abnormalities. They show increased aggressive, anxiogenic and depressive-like behavior and as well as anhedonia.

5 Health

A hundred years ago, the leading cause of death in America was infectious disease (http://www.cdc.gov/nchs/fastats/lcod.htm). As public health improved and antibiotics were developed, people lived longer. As a result, the leading causes of death today belong to the category “age related illnesses”. They included cardiovascular diseases [Steffens et al., 2005] (heart attack (#1 cause of death) and stroke (#3)), neurological diseases[Milton, 2002][Ramirez et al., 2005] [Hill and Gorzalka, 2005] (Alzheimer’s (#8), depression), immune disorders (diabetes[Li et al., 2001] (#6), multiple sclerosis[Shohami and Mechoulam, 2006], Crohn’s Disease[Massa and Monory, 2006]), and cancer[Guzman, 2003] (#2). (http://www.cdc.gov/nchs/fastats/lcod.htm) There are numerous peer-reviewed studies that indicate a beneficial affect on all these conditions can result from activating the cannabinoid system. The endocannabinoid system regulates all body systems (cardiovascular, digestive [Izzo and Coutts, 2005], endocrine [Maccarrone and Wenger, 2005], excretory [Brady et al., 2004], immunological [Carrier

et al., 2005], musculo-skeletal [Casanova et al., 2003] [Ofek et al., 2006], neurological [Fride, 2005], tegumentary [Casanova et al., 2003], reproductive [Wang et al., 2006]), and through these systems regulates body temperature [Hollister, 1971], food intake [Cota et al., 2005], sleep, reproduction [Wang et al., 2006], pain [Burns and Ineck, 2006] and mental attitude [Piomelli et al., 2006]. In fact, mice knocked out for their CB1 receptor have shortened life spans [Zimmer et al., 1999]. Therefore, in keeping with man's evolutionary history in which endocannabinoids are found in the most evolutionarily advanced areas of the brain, it appears that the need to extend the cannabinoid system is still with us.

6 Politics

This section will speculate on a possible relationship between a person's cannabinoid system and their politics by extending research findings, done largely with mice, to humans. Furthermore it will speculate as to what behavior might emerge as the level of cannabinoid activity rises in the population. The rise in cannabinoid activity can occur slowly through genetic changes that effect endocannabinoid levels, or more rapidly through the consumption of the essential fatty acid precursors to endocannabinoids, and through marijuana consumption.

It is now known that the brain has the capacity to regenerate nerve cells, and that this process is largely controlled by endocannabinoids [Jiang et al., 2005]. Furthermore, regeneration is involved in neuronal plasticity and learning [Chevaleyre et al., 2006]. It is hypothesized that people with an endocannabinoid deficiency in critical areas of the brain will tend to look backwards in time because that view minimizes the need for re-learning. Conversely, a robust endocannabinoid system equips an individual to adjust to the future by controlling the reformulation of old memories and patterns of behavior as new learning dictates.

It is self-evident that in a population there will be some who are more endowed with endocannabinoid activity than others. The relative level of endocannabinoid activity can vary from one tissue to another depending on an individual's genetics and environmental history. Individuals with a relative endocannabinoid deficiency in critical areas of the brain will have a greater tendency to agree with one and other because they have a greater probability of looking into the past and trying to preserve the status quo. In contrast, individuals endowed with an above average endocannabinoid system can better adjust to the novelty of a developing situation. They will have a greater tendency to optimistically look into the unknowns of the future because they have the adaptive biochemical machinery.

The greater tendency for conservative consensus will tend to give the cannabinoid deficient population greater political power. As a result, they will preferentially gather in government (somewhat independent of political party). As a result, if this hypothesis is true, people with relatively lower endocannabinoid activity are the same individuals who make laws against marijuana use, even for medicinal purposes. The biological activity of cannabinoids goes against their genetics. They make law independent of facts to the

contrary despite overwhelming scientific evidence that supports the voice of thousands who use marijuana medicinally. For example, the FDA announcement in April of 2006 that marijuana has no medical value

7 Conclusions

Because of the broad impact that politically motivated policy has on all aspects of our lives, the war on marijuana is actually an example of evolution in action. Mankind is engaged in a genetic battle based on genetically defined behavioral determinants. The ability of cannabinoids to reduce age-related illnesses, and also to regulate open mindedness [Hill et al., 2006]emphasizes the importance of having marijuana available for the health and survival of a population. The rapidly changing world that we live in, with its associated possible dangers for the survival or our species (global warming, nuclear warfare, pandemic diseases), demands that the population as a whole work cooperatively to promote policies that are responsive in a timely manner to changes that potentially threaten the very survival of mankind.

As the cannabinoid activity in the human population increases, what emergent behavior might result? If humans consume essential fatty acids so that they can maximize their endocannabinoid production, and consume appropriate amounts of supplemental marijuana, they should became less depressed [Denson and Earleywine, 2006], more optimistic and forward-looking, less subject to age related illnesses, suffer less pain and become more cooperative. The dissipative structures that are our political, economic, religious and social systems might undergo drastic character changes, perhaps for the betterment of all.

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