Role of the Endogenous Communication System (eCS) in the Resolution of Chronic Pain

Robert Rager, BA Chemistry

Tama Copeman, PhD

Zachary Phillips, PharmD

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*Contact Author, email: bobrager@comcast.com

ABSTRACT

The resolution of inflammation is an active process controlled by endogenous mediators with selective actions on neutrophils and monocytes. The initial phase of the acute inflammatory response is characterized by the production of pro-inflammatory mediators followed by a second phase in which lipid mediators with pro-resolution activities may be generated. Failure to resolve inflammatory debris is, among other issues, associated with chronic inflammation. Current approaches to pain management do not address resolving chronic inflammation, nor injury repair. Widespread use of NSAIDs, for example, inhibit autocoids and further complicate resolution. Novel approaches involving redundancy of multimodal alternative pathways simultaneously involved in the pain mitigation process, are logically justifiable

INTRODUCTION

Persistent pain in neuropathic conditions is often resistant to conventional analgesic therapy, providing most patients with only partial, if any, symptomatic relief (1). Chronic pain is a frequent condition calling for improved analgesics, and it affects an estimated 20% of people worldwide (2,3). Treatment of such complex pain with one or a combination of two analgesics at the most is typical, although generally inadequate (4,5)

It seems prudent to make use of endogenous repair and homeostasis mechanisms, already available in the body. Cannabinoids, classified as endogenously produced and locally acting autacoids, are scientifically recognized as natural anti-inflammatory compounds with superior efficacy versus NSAIDs (non-steroidal anti-inflammatory drugs) that decrease pain (6) and lower fever. In higher doses Cannabanoids decrease pain but without well-known negative side effects of long-term use. These include risk of serious gastrointestinal side effects such as perforation, ulceration, or bleeding (7,8). Current chronic pain treatments have numerous shortcomings. Tolerability, addiction and overdose potential, and serious adverse effects often limit their use over an extended period, and the pain control achieved by such drugs are often not ideal (7). Even the effects of often-prescribed drugs such as pregabalin or opioids are disappointing for

patients suffering from neuropathic pain. Furthermore, some classes of analgesics might decrease pain, but can also negatively interfere with our body repair systems, such as the non-steroidal anti-inflammatory drugs (NSAIDs) including cyclooxygenase (COX) inhibitors.

While it is widely known these last compounds inhibit pro-inflammatory cascades in many chronic pain states. Much less known is that the same inhibition impairs the biological activity of endogenous repairing and protecting molecules, such as the lipoxins and the resolvins. These molecules with "pro-resolving" properties are representative of the temporal cellular and biochemical events in the onset and resolution of inflammation (9,10). The early phase of inflammation is characterized by the release of pro-inflammatory mediators and extravascular accumulation of neutrophils, followed by infiltration of monocytes that differentiate into macrophages. This phase is characterized by the formation of anti-inflammatory and pro-resolution mediators, e.g., lipoxins (LXs) and resolvins. These mediators stop further neutrophil trafficking and facilitate the removal of inflammatory debris such as apoptotic cells. The macrophage ingestion of apoptotic cells results in potent anti-inflammatory effects through the production of anti-inflammatory cytokines such as TGF-β1, IL-10 and PGE2, as well as the decreased release of pro-inflammatory mediators, including IL-8, TNF-α and TXA2 (11).

TAMING INFLAMMATION REQUIRES RESOLUTION AND A ROBUST eCS

The resolution of inflammation is an active process controlled by endogenous mediators with selective actions on neutrophils and monocytes. The initial phase of the acute inflammatory response is characterized by the production of pro-inflammatory mediators followed by a second phase in which lipid mediators with pro-resolution activities may be generated. The identification of these mediators has provided evidence for the dynamic regulation of the resolution of inflammation. Among these endogenous local mediators of resolution, LXs, lipid mediators typically formed during cell–cell interaction, were the first to be recognized. More recently, families of endogenous chemical mediators, termed resolvins and protectins, were discovered (12).

LXs and aspirin-triggered LXs are considered to function as 'braking signals' in inflammation, limiting the trafficking of leukocytes to the inflammatory site. LXs are actively involved in the resolution of inflammation-stimulating non-phlogistic phagocytosis of apoptotic cells (also known as inflammatory debris) by macrophages, . Furthermore, LXs have emerged as potential anti-fibrotic mediators that may influence pro-fibrotic cytokines and matrix-associated gene expression in response to growth factors (10). Further, DHA Omega 3 assists resolvins and related compounds (e.g., protectins) through pathways involving cyclooxygenase and lipoxygenase enzymes to resolve the inflammatory responses. Failure to resolve inflammatory debris is, among other issues, associated with chronic inflammation.(13)

NSAIDs inhibit the synthesis of many autacoids - a class of natural compounds which are generated only as-needed and act as tissue hormones and natural pain relievers, thus NSAIDs do not contribute to resolving chronic inflammation, nor do they repair injury (14). Not only NSAIDs negatively influence inflammatory resolution. Opioids are also increasingly recognized as pro-inflammatory compounds. Opioid-induced glial activation and its pro-inflammatory consequences are regarded as factors for failure of analgesia as well as a pathogenetic base for the emergence of opioid tolerance (15,16). In all of these cases analgesics negatively interfere with endogenous autacoid repair and anti-inflammatory processes (6). New inroads in the treatment of chronic pain via the autacoids seems like a promising way of identifying new analgesic compounds, acting via endogenous healing mechanisms. It seems indeed quite logical to make use of endogenous repair and homeostasis mechanisms, already available in the body. Autacoid Medicine may be a new paradigm for the design of the 21st century pain medicine (18).

Cannabinoids, particularly endocannabinoids (e.g., PEA), their cannabinoid receptors and enzymes that construct and deconstruct the neurotransmitter cannabinoids only as needed, comprising the Endocannabinoid System (eCS), are responsible for regulating homeostasis via signaling throughout the central and peripheral nervous systems. Furthermore, cannabinoids interacting, directly or indirectly, with CB2 receptors are scientifically recognized as natural anti-inflammatory, anti-pain autacoid compounds. These anti-inflammatory cannabinoids uniquely act on the immune system

through the mammalian endogenous communication system known as the eCS (22) with superior efficacy versus NSAIDs. Both cannabinoids and NSAIDs are shown to decrease pain (6) and lower fever, but cannabinoids achieve this without any well-known negative side effects of long-term use. Long-term risks of NSAID use include not only serious gastrointestinal side effects. According to a recent meta-analysis, the potential increased risk of coronary heart disease is significant (19,20).

CLINICAL ENDOCANNABANOID DEFICIENCY

But because of life stresses, both internal (e.g., oxidative stress) and external (e.g., environmental, as well as, psychological stress) to living mammals over the lifespan, the Endocannabinoid System (eCS) can become less efficient due to diminished performance, or availability, of any and/or all the eCS components (i.e., receptors, neurotransmitters and their associated enzymes) (23). Diminished eCS performance can lead to an overall disruption of homeostasis and therefore chronic, systemic inflammation, poor wellness and over the lifespan, painful age-related discomforts (23).

Diminished homeostasis leads to increased inflammation which can result in damaged tissues, nerves, and joints, often associated with age related discomfort. Chronic conditions of diminished eCS performance from life stresses, illnesses and aging have been described as Clinical Endocannabinoid Deficiency (CECD). Several otherwise unexplained conditions including, but not limited to, migraine, irritable bowel syndrome, autoimmune-mediated maladies, and fibromyalgia have been attributed to CEDC (23,24,25).

The NIH has patented the Cannabis derived compound CBD (Cannabidiol) for its antioxidant and anti-inflammatory properties (26). Subsequent research has established CBD as an effective anti-inflammatory plant-derived phyto-cannabinoid compound for use in pain mitigation related to tissue and nerve damage typically due to inflammation in mammals. CBD is also known to help sustain a robust body-wide endoCannabinoid (eCB) System Tone (eCS Tone) based on optimal performance of the various components of the “classic” endocannabinoid system (eCS) (i.e.,

cannabinoid receptors CB1 and CB2, the eCB neurotransmitter ligands ANA and 2-AG, and their metabolic enzymes FAAH or MAGL) (27,28).

Cannabis as a genus (i.e., both Marijuana and Hemp plant families) has been classified by the US Drug Enforcement Administration (DEA) as a Class 1 Controlled Substance. 'Marijuana', the Cannabis plant family with flowers containing naturally significant quantities of psychoactive THC (Tetrahydrocannabinol) and nominal amounts of non-psychoactive CBD. Hemp plants, the Cannabis plant family with strong fibers (legally classified as Industrial Hemp) have naturally significant amounts of CBD but only trace amounts of THC (<0.3% dry weight). As a result of strict DEA classification of all of Cannabis instead of only THC-laden Marijuana, has caused a hopelessly confusing condition regarding CBD legality resulting in tightly controlled limits on CBD research as well as a total lack of federal regulations required to ensure FDA product safety labeling. Because of the many positive wellness related effects of CBD acting on the eCS, CBD has attracted considerable attention and interest from the public (29). The key influence of CBD is on the endogenous signaling process of homeostasis that maintains physiological/biochemical balance necessary for wellness in all living mammals (30).

All vertebrate animals have an endoCannabinoid system (eCS). In fact, the eCS is ubiquitous in nearly all animals from mammals to the more primitive phyla such as Cnidaria; the early emergence of the eCS in the evolution of the Phyla, and its conservation throughout the millennia, indicates its long-standing biological importance (31). The eCS, providing homeostatic balance after various stresses to the nervous, immune, and other organ systems, opened the door to novel approaches for the management and treatment of inflammatory and immune-related disease states (32).

The eCS consists of three parts: (1) endogenous ligands, (2) G-protein coupled receptors (GPCRs), and (3) enzymes to construct, degrade and recycle the ligands. Four endogenous cannabinoid molecules have been identified as ligands in the eCS to date: ANA (anandamide (or arachidonoylethanolamide), 2-AG (2-arachidonoyl glycerol), OEA (oleoylethanolamide), and PEA (palmitoylethanolamide). Three G-coupled protein receptors have been described (CB1, CB2, now including GPR55 - aka CB3), with others being considered (e.g., GPR119) (33). Coincidentally, the phytochemicals are produced in large quantities by the

Cannabis Sativa L plants (predominantly CBD in Hemp and THC in Marijuana). These plant-based cannabinoids (termed phytocannabinoids) can interact with this system as ligands (31,34).

The eCS is a biological signaling system involved in regulating various physiological and biological dynamic balancing processes (homeostasis) in all mammals. Furthermore, the eCS is essential to CNS homeostasis and plays a significant role in the regulation of the inflammatory processes and pain signaling.(35) The endocannabinoid system has been shown to have a homeostatic role (i.e., steady internal dynamic biochemical balancing conditions) by controlling several metabolic functions, such as energy storage and nutrient transport (35). Homeostasis - the dynamic state of equilibrium management concerning the constancy of the internal environment in which the cells of the body live and survive - defines the condition of optimal functioning for the organism, or wellness. Equilibrium variables of great importance to proper body function include body temperature, fluid balance, and rates of gas exchange. Other variables include the pH of extracellular fluid, the concentrations of sodium, potassium and calcium ions, as well as that of the blood sugar level all needing to be regulated despite changes in the environment, diet, health, or level of activity (35).

Each of these variables is controlled by one or more regulators or homeostatic mechanisms, which together maintain the living organism (e.g., mammal). Optimum health and wellness depend on robust operational tone, or efficiency, of the eCS to regulate homeostasis throughout the mammalian lifespan. Disruption of homeostasis due to oxidative stress, disease, aging, inflammation (32) or other conditions of modern life can result in reduced eCS performance or poor eCS Tone, yielding various age-related discomforts in which pain is typically involved (35). Certain painful conditions have been positively associated with Clinical Endocannabinoid Deficiency (CECD). Emerging literature documents CECD as an etiology in migraine, fibromyalgia, irritable bowel syndrome, psychological disorders, and of other illnesses and conditions potentially contributing to various additional age-related discomforts.(24)

The best-known natural endogenous endocannabinoids are anandamide (ANA), 2 acyl-glycerol (2AG) and palmitoylethanolamide (PEA).(36) These naturally produced bioactive lipid autocoids are capable of interacting

directly or indirectly with the endocannabinoid receptors such as CB1,, CB2, and CB3 (aka GPR55), the activation thereof is responsible for different properties including, but not limited to, anti-inflammatory, antioxidant and analgesic properties. These receptors are sensitive to endogenous cannabinoids, as well as phytocannabinoids and certain related compounds derived from plants and/or cannabinoids of synthetic derivation, which belong to receptors coupled to protein G (37).

CB1 and CB2 receptors are structurally similar. CB1 receptors are abundant in the central nervous system, particularly the hippocampus and associated cortical regions, in the brain and in the basal ganglia. CB2 receptors are abundant in the gut and peripheral nervous system mostly associated with the immune system. CB2 receptors being primarily present in T cells, the mastocytes, B lymphocytes and at the level of the hematopoietic cells as well as in the peripheral nervous terminations, play a key role in the antinociceptive, antalgic and anti-inflammatory activity. Endocannabinoids of natural origin, including PEA, represent an important alternative to the traditional anti-inflammatory drugs treating inflammation (brain neuro-inflammation or other types of inflammatory conditions) and in all conditions characterized by painful symptomatology (30). PEA's protective effects are mediated by its cellular targets, including direct activation of CB3 (i.e., GPR55) and PPAR-a receptors and the indirect activation of cannabinoid receptors CB1 and CB2 and TRPV1 channels (38,39). CBD and THC are natural phytocannabinoid compounds in Cannabis (plant families commonly known as Marijuana and Hemp). CBD and THC are mammalian CB (cannabinoid) receptor agonists that have been used to reduce pain in humans for millennia. But THC is psychoactive and its use and research into its mechanism of action have been severely limited by the Drug Enforcement Administration (DEA) listing of Cannabis, including CBD, as a continuing Class 1 Controlled Substance for many decades.(38) Recent studies indicate potential damage to the fetus of pregnant women using CBD, especially inauthentic CBD oils that may contain heavy metals that cannabis is good at extracting from the soil (40).

Because, in 2018, CBD became an FDA approved drug (i.e., CBD isolate product for pediatric seizures known as Epidiolex®) (41), CBD and other Cannabis derived phytocannabinoids (i.e., THC) are currently entangled in

State and Federal legal issues, alternative approaches to maintaining robust eCS tone functioning into old age are necessary and desirable.

TOWARD PAIN RESOLUTION WITH A NON-CLASSICAL ENDOCANNABINOID

Endogenous endocannabinoids show promise. Palmitoylethanolamide (PEA) is a non-classical endocannabinoid (autacoid) bioactive lipid mediator belonging to the N-acyl-ethanolamine (NAE) fatty acid amide family (42). Synthesized on demand within the lipid bilayer (43) it acts locally (44) and is found in all tissues including the brain (45). PEA is thought to be produced as a pro-homeostatic protective response to cellular injury and is usually up-regulated in disease states. Its pleiotropic effects include anti-inflammatory, analgesic, anticonvulsant, antimicrobial, antipyretic, anti-epileptic, immunomodulatory and neuroprotective activities (46).

PEA's multi-faceted effects are due to its unique mechanisms of action that affect multiple pathways at different sites (44) primarily targeting the nuclear receptor peroxisome proliferator-activated alpha (PPAR-a), PEA also acts on novel cannabinoid receptor, CB3 - G protein-coupled receptor 55 (GPR55) and G protein-coupled receptor 119 (33,36,47,48,49).The cannabinoid receptor CB3 plays a role in mechanical hyperalgesia associated with inflammatory and neuropathic pain (50). Moreover, PEA indirectly activates cannabinoid receptors CB1 and CB2 through inhibiting the degradation of the endocannabinoid, anandamide (ANA), a phenomenon known as the "entourage effect" (43).

However, given the redundancy and complex nature of the underlying pathogenesis, therapies are expected to incorporate more than PEA for optimal efficacy. Multi-modal, alternative pathways including a variety of receptors, neurotransmitters and regulatory systems participate in the pain process (51). Therefore novel approaches involving redundancy of multimodal alternative pathways simultaneously involved in the pain mitigation process, are logically justifiable as a unique approach (52).

SUMMARY

The Endocannabinoid System is a natural endogenous communication system in all mammals that regulates homeostasis. Homeostasis represents the dynamic balancing of biological processes necessary for proper operation and therefore wellness to persist throughout the lifespan. A major portion of the eCS is located in the microbiome where the immune system is also resident. Inflammation is considered a necessary 'far from homeostasis' condition. However, if it is not controlled and resolved, it can become the source of chronic inflammation leading to long term tissue and nerve damage, resulting in various age-related discomforts. Natural endogenous cannabanoids act in a retrograde manner to down-modulate inflammation and pain signals to the brain and offer potential for improved therapeutic approaches.

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