REVIEW ARTICLE

The Endocannabinoid System and its Modulation by Cannabidiol (CBD)

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ABSTRACT

The endocannabinoid system (ECS) is an extensive endogenous signaling system with multiple elements, the number of which may be increasing as scientists continue to elucidate its role in human health and disease. The ECS is seemingly ubiquitous in animal species and is modulated by diet, sleep, exercise, stress, and a multitude of other factors, including exposure to phytocannabinoids, like Cannabidiol (CBD). Modulating the activity of this system may offer tremendous therapeutic promise for a diverse scope of diseases, ranging from mental health disorders, neurological and movement disorders, pain, autoimmune disease, spinal cord injury, cancer, cardiometabolic disease, stroke, TBI, osteoporosis, and others. (*Altern Ther Health Med.* 2019;25(S2):6-14.)

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As interest in, and use of, phytocannabinoids from *Cannabis Sativa L* (Cannabis) has increased with the number of state-regulated *Cannabis* programs, heightened scientific attention has been directed toward the mechanisms by which delta-9-tetrahydrocannabiniol (delta-9-THC), cannabidiol (CBD), and other phytocannabinoids exert their physiological effects in the body. These exogenous, plant-derived ligands interact with endogenously produced proteins, receptors, enzymes, and endogenous ligands, in one of the most evolutionarily preserved biological systems known to the life sciences, the endogenous cannabinoid signaling system or endocannabinoid system (ECS).

The ECS is thought to be 600-million-years-old. Present in every animal species, except insects, it evolved as a stress/harm regulation network that functions to restore homeostasis following cellular stressors.[1] The ECS is upregulated and downregulated on a continuous basis as needed. It communicates with all other systems in the body and has been implicated in multiple regulatory functions in both health and disease, including pain, perception, mood, memory, and reward.[2,3] This vital physiological system is modulated by diet, sleep, exercise, stress, and a multitude of other factors, including exposure to phytocannabinoids. According to George Kunos, Scientific Director of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) at the National Institutes of Health (NIH), "Modulating endocannabinoid system activity may have therapeutic potential in almost all diseases affecting humans."

The discovery of the ECS began with the search for the active ingredient in *Cannabis*.[4] CBD was first isolated from a *Cannabis* extract in 1940.[5] Initially, CBD was deemed an inactive constituent because it failed to mimic the effects of *Cannabis* extracts in animals and humans.[6] As a result, it wasn't characterized structurally until 1963, more than 20 years later.[7]

Delta-9-tetrahydrocannabinol (THC) was isolated and characterized a year later, in 1964.[6] Delta-9-THC does mimic the effects of a *Cannabis* extract, and subsequently, became the focus of phytocannabinoid research going forward.[8] In addition to investigating its stereochemistry, pharmacokinetics, and other characteristics, scientists began to explore the pharmacology of delta-9-THC, specifically its mechanisms of action.

With the endogenous opioid system as a blueprint, a G-protein-coupled receptor (GPCR), to which delta-9-THC exhibited partial agonism, was identified in 1988.[9] The discovery of this receptor, cannabinoid receptor 1 (CB1), paved the way for the detection of endogenous ligands that demonstrated affinity for the receptor.

The endocannabinoid anandamide—N-arachidonoylethanolamine, also known as AEA—was subsequently identified in 1992,[10] and a second endocannabinoid, 2-Arachidonoylglycerol (2-AG), was discovered in 1995.[11] A second, peripheral cannabinoid receptor (CB2) was identified in 1993.[12] Investigations into the production and breakdown of endocannabinoids were also being conducted during this time. The enzymes responsible for synthesizing and degrading anandamide and 2-AG were identified in 1994 and 1993, respectively.[13,14]

ENDOCANNABINOIDS

Endocannabinoids are the signaling molecules of the endocannabinoid system. They are fatty-acid neurotransmitters that safeguard body systems by coordinating and fine-tuning intracellular biochemistry and intercellular communication across all physiological systems without exception. A multitude of pathological conditions may involve alterations in endocannabinoid synthesis or degradation, receptor expression, enzyme function, and a variety of other factors.[15]

While anandamide and 2-AG are the most studied endocannabinoids, other endocannabinoid-like mediators that aren't formally classified as endocannabinoids, such as oleoylethanolamine (OEA) and palmitoylethanolamine (PEA), also exist. Endocannabinoids primarily mediate their effects through interactions with receptors, including non-cannabinoid receptors, and with other underlying mechanisms. Endocannabinoids share some chemical characteristics with phytocannabinoids, but they are structurally different and generally have a lesser degree of affinity for cannabinoid receptors.[16] Also, like their phytochemical counterparts, endocannabinoids are *promiscuous* ligands, meaning they interact with a broad range of non-cannabinoid receptors.[17]

Unlike conventional neurotransmitter systems, endocannabinoids are lipids, as opposed to peptides like dopamine, gamma-aminobutyric acid (GABA), and acetylcholine. They are synthesized on demand, typically in postganglionic neurons, as opposed to being synthesized a priori and stored in vesicles in preganglionic neurons. Also, unlike conventional neurotransmitter systems, in which neurotransmitters diffuse from preganglionic to postganglionic neurons, endocannabinoids diffuse in a reverse or retrograde direction, exerting their effects through receptors on preganglionic neurons. This review discusses the dynamics of this system in greater detail below.

Anandamide

Anandamide is a high-affinity, partial agonist of CB1 and CB2 receptors—Ki: 400 ± 120nM and 1760 ± 360nM, respectively.[15,16,18] Research has shown that it can inhibit adenylyl-cyclase activity intracellularly at both receptors.[16] In fact, cannabinoids in general appear to act on the adenylate-cyclase, second-messenger pathway in an inhibitory fashion.[4]

Like most other lipid mediators, endocannabinoids have more than just one set of biosynthetic and degrading pathways and enzymes.[3] Anandamide is predominantly synthesized by the enzyme N-acyl-phosphatidylethanolamine phospholipase D (NAPE-PLD) and hydrolyzed intracellularly by fatty acid amide hydrolase (FAAH) and secondarily by *N*-acylethanolamine-hydrolyzing acid amidase (NAAA). In humans, a second enzyme, known as FAAH-2, hydrolyzes anandamide at lower rates than FAAH.

A group of fatty-acid-binding proteins (FABPs) has been shown to be the intracellular transporter for anandamide and 2-AG from the cell membrane through the cytosol for hydrolysis at the endoplasmic reticulum.[19] The role of FABPs is discussed further below.

2-AG

This endocannabinoid is very similar to anandamide in chemical structure; however, it's a moderate-affinity, full agonist at CB1 and CB2—Ki: 472 ± 55nM and 1400 ± 172nM, respectively.[15,16,18] It's synthesized and hydrolyzed by different enzymes, namely diacylglycerol lipase (DAGL) and monoacylglycerol lipase (MAGL), respectively.[20] This endocannabinoid is the most abundant one in the central nervous system (CNS) and plays a major role in CNS development and synaptic plasticity.[21]

Independent Regulation of 2AG and Anandamide

Tissue levels of 2AG and anandamide are independently regulated, allowing the two signaling molecules to exert different functions even within the same cell, tissue, or organ system.[15] Both pathological and normal physiologic conditions can alter concentrations of only one, or both of these molecules, and opposing changes in the levels of anandamide and 2AG are not uncommon. Endocannabinoids not only interact with cannabinoid receptors, they are involved in cellular tuning and homeostasis through coordinated interactions with more than one target at any one time.[2,15]

ECS RECEPTORS

Cannabinoid receptors are 7-transmembrane-domain GPCRs. CB1 and CB2 receptors differ in their amino-acid sequence, anatomic distribution, mechanisms of signaling, and other characteristics.[16] G-protein receptors represent the most common receptor system in vertebrates, and CB1 receptors are the most abundant and densely concentrated receptors in the human CNS.[22,23] Some researchers have postulated that *cannabinoid receptor* may be a misnomer given that THC and THC-V are the only phytocannabinoids that exhibit high affinity for the CB1 and CB2 receptors.[15] Practically speaking, however, ligands that exhibit even low affinity are deemed cannabinoids, including CBD, which

demonstrates negligible affinity for either CB receptor—CBD: Ki at CB1 = 4350 nM; CB2 = 4200 nM.[24]

Cannabinoid Receptors

CB1 receptors. The CB1 receptor is widely distributed throughout the CNS, particularly in nociceptive areas of the brain and spinal cord but also on certain cells of the immune system, adipose tissue, liver, muscle, reproductive cells, kidney, and lungs.[22,25,26]

These receptors are noticeably absent in the cardiac and respiratory centers of the brainstem,[27] which is why cannabis doesn't depress respiration or stop the heart from beating. Respiratory depression, mediated by opioid receptors in the respiratory center in the brainstem, is the most common cause of opioid-overdose mortality.[28] Respiratory depression isn't a risk with phytocannabinoids.

CB2 receptors. In contrast, CB2 receptors are mainly located in the periphery, in lymphoid and immune tissues and on organs like the heart and liver.[29] Surprisingly the CB2 receptor has only 44% chemical homology with the CB1 receptor.[12]

The predominance of CB2 receptors in immune tissues underlies the immunomodulatory role of the ECS, with one of its key functional benefits occurring in the presence of inflammation.[30,31] Modulation through the CB2 receptor might provide an avenue for the treatment of various inflammatory processes.[32]

Interaction of cannabinoid receptors. Individual cannabinoid receptors interact with one another, and with non-cannabinoid receptors, such as opioid receptors,[33,34] forming heteromers that alter the pharmacodynamics of the individual subunits. These heteromers have demonstrated bidirectional cross-antagonism, whereby CB1 antagonists block the effects of CB2 agonists and enable CB2 antagonists to block CB1 agonists.[35]

Non-cannabinoid Receptors

GPR55 receptors. Work by a number of groups of researchers in recent years has provided evidence that the ECS is more complicated and expansive than previously thought. In fact, researchers have hypothesized that the G-protein receptor 55 (GPR-55) may be a third cannabinoid receptor due to its affinity for endo- and phytocannabinoids.[3,36,37] GPR55 receptors are also G-GPCRs and are widely distributed in the brain and periphery. They regulate multiple physiological processes that influence motor activity, movement coordination, nociception, energy expenditure, bone metabolism, anxiety modulation, and more.[37,38] Activation of this receptor is positively associated with obesity in humans.[37] Additionally, the GPR55 receptor is expressed in various cancer types.[39]

TRPV1 receptors. The transient receptor potential, cation channel subfamily V member 1 (TRPV1), also known as the capsaicin receptor and the vanilloid receptor 1, has also received some consideration as a cannabinoid receptor.[3] While TRPV1 was first identified as a receptor for capsaicin, a pungent ingredient in hot chili pepper, it's also activated by vanilla-like compounds as well as compounds in ginger, black pepper, and other botanicals.[40,41] Anandamide is a full agonist at the TRPV1 receptor, and 2-AG has also been shown to activate TRPV1, although at concentrations much higher than anandamide.[3] CBD has been found to be a weak, full agonist of TRPV1.[42]

TRPV1 expression occurs mainly in sensory nerves. The activation of TRPV1 receptors causes terminals of central and peripheral sensory nerves to release neuropeptides, resulting in smooth-muscle contraction, cough, pain, and neurogenic inflammation.[43]

5-HT/serotonin receptors. The 5-hydroxytryptamine receptors, or 5-HT or serotonin receptors, are a class of GPCRs and ligand-gated ion channels found primarily in the central and peripheral nervous systems. Serotonin, the predominant endogenous ligand, is a biogenic monoamine and is similar in structure to histamine, dopamine, epinephrine, and norepinephrine. In the CNS, serotonin mediates both inhibitory and excitatory neurotransmission via a variety of serotonin receptors, of which 14 types exist.[44]

The 5-HT receptors are present in the GI tract, brain, platelets, lung, kidneys, and other tissues. These receptors are implicated in a wide range of biological activity including pain perception,[45] nausea and vomiting,[46] anxiety,[47] addiction, appetite, and sleep.[48] Recent studies have begun to examine interactions between the ECS and serotonergic systems, primarily due to the fact that both play roles in the regulation of stress and other emotional processes, including body temperature, feeding behavior, sleep, and arousal.[41]

Adenosine receptors. Adenosine receptors are a group of GPCRs to which adenosine binds as an endogenous ligand. Caffeine and theophylline are known to serve as exogenous antagonists producing the stimulating effects of coffee, tea, and chocolate.[49] In humans, 4 types are known—A1, A2A, A2B and A3, each encoded by different genes. These different receptor types possess distinct areas of localization, different means of regulation, and different signal transduction pathways.[50]

Adenosine receptors provide broad anti-inflammatory effects.[51] In the CNS, adenosine provides neuroprotection during hypoxic, ischemic, and oxidative events. Additionally, adenosine modulates synaptic plasticity and neurotransmitter release. Adenosine also plays an important role in the regulation of sleep and the development of various cancers.[52]

PPAR-alpha receptors. The family of transcription factors termed peroxisome proliferator-activated receptors (PPAR) are type II nuclear receptors with 3 isoforms: PPAR-alpha, PPAR-gamma, and PPAR-delta.[53] PPARs promote the transcription of specific genes upon activation by small lipophilic ligands. They play an essential role in energy homeostasis and metabolic function, and thus, are localized in most tissues, including liver, skeletal muscle, cardiac, bone, endothelial, and other tissues.[54] In addition, PPAR activation has been shown to play a role in neuroprotection, reward pathways, memory and cognition,

analgesia, inflammation and immunity, and vasoregulation as well as the regulation of feeding and satiety.[55,56]

PPAR-alpha is activated by endocannabinoids, endocannabinoid-like compounds—oleoylethanolamine (OEA) and palmitoylethanolamine (PEA)), phytocannabinoids, and synthetic cannabinoid ligands.[55] Substantial evidence now exists that cannabinoids induce apoptosis in many cancer cell lines via PPARγ receptors.[55]

NEUROREGULATION AND PROTECTION

Among other functions, the ECS is a neuroregulatory system that maintains and restores homeostasis by modulating the release of neurotransmitters, both excitatory and inhibitory. Neuromodulation, or neuroregulation, is an exceptionally important physiological phenomenon, and CB1 activation always reduces neurotransmitter release, regardless of the transmitter involved.[57]

During an action potential, depolarization of a postganglionic neuron results in increased intracellular calcium levels, which triggers the synthesis of endocannabinoids in the postganglionic neuron. These endocannabinoids are then released into the synapse and diffuse in a retrograde direction to bind to CB1 receptors on axon terminals in the preganglionic neuron, a negative feedback process called retrograde inhibition or depolarization-induced suppression of excitation and inhibition.

Seizure Disorders

Depolarization-induced suppression of excitation is one of the ways that the ECS protects the nervous system from hyperactivity during seizure events.[58] Endocannabinoids are produced during seizures and act on cannabinoid receptors in the hippocampus and neocortex.[57] Inhibition of glutamate by endocannabinoids can dampen seizure activity and reduce neuronal death.[57] Phytocannabinoids are generally anticonvulsant and have been referred to as circuit breakers because of their ability to reduce seizures and corresponding neurodegeneration.[57,59]

In June 2018, the FDA approved purified CBD as the drug product Epidiolex (Greenwich Biosciences, Carlsbad, CA, USA) to treat 2 severe forms of epilepsy—Lennox–Gastaut syndrome and Dravet syndrome.[60-63] The anticonvulsant effects of CBD aren't confined to these rare forms of epilepsy. Anticonvulsant and neuroprotective effects have been demonstrated in animal models of status epilepticus[22] and in humans with generalized epilepsy and treatment-resistant epilepsies.[64-66]

Traumatic Brain Injury (TBI)

Cannabinoids also have the ability to protect neurons from a variety of insults resulting from TBI, such as calcium influx, excitotoxicity, free radical formation, and neuroinflammation.[67] In-vivo and in-vitro data suggest that the endocannabinoids anandamide and 2-AG serve as homeostatic regulators to limit brain damage following brain injury.[68,69] Furthermore, exogenous cannabinoids given within 4 hours of TBI, have been shown to limit glutamate toxicity and nerve-cell damage in an animal model.[68]

Ischemic Events

As with seizure and TBI, the body's levels of endocannabinoids spontaneously elevate during stroke, presumably indicating a protective response.[70] In experimental models of stroke, cannabinoids significantly reduced infarct size and improved functional outcomes in animals.[71] Neuroprotection exerted by exogenous 2-AG suggests that the formation of 2-AG may serve as a molecular regulator of pathophysiological events in the brain.[68] CBD appears to provide stronger neuroprotection than delta-9-THC via a CB1-independent mechanism.[72] In a study of ischemia produced by carotid artery occlusion, CBD demonstrated a protective effect on neuronal death in mice.[73]

Autocrine and Paracrine Function

A lesser known function of the endocannabinoid system is regulation of homeostasis via autocrine and paracrine signaling. Autocrine regulators are substances produced by a cell that regulate the cell itself. Autocrine regulation is classically modeled in liver regeneration where autocrine signaling triggers the regrowth of liver cells.[74] Paracrine regulators are substances produced by a cell that regulate nearby cells. Paracrine regulation is classically modeled in immune activation of T-cells, B-cells, or NK cells. Paracrine signaling is also highly involved in the wound-healing process.[75]

Gastrointestinal Function

In addition to acting as neurotransmitters do, endocannabinoids also act as autocrine and paracrine regulators. For example, in the presence of inflammatory bowel disease (IBD), immune cells, such as mast cells and macrophages, infiltrate the muscular and mucosal layers of the gastrointestinal (GI) tract and secrete inflammatory mediators, such as cytokines and chemokines like TNF-alpha. The presence of these chemicals stimulates the production of endocannabinoids, which act on cannabinoid and non-cannabinoid receptors, such as TRPV1, on both the immune cells producing the endocannabinoids (autocrine regulation) and the nearby immune cells (paracrine regulation).[76] The overall effect is a decrease in the production of inflammatory chemicals, and ultimately, reduced infiltration of other inflammation-producing white bloods cells.

An expanding body of research has demonstrated that cannabinoids also play important roles in normal gastrointestinal physiology. For example, anandamide and delta-9-THC inhibit intestinal motility, delay of gastric emptying, and decrease of gastric secretion, potentially by activating CB1 receptors in cholinergic pathways.[77] The anti-emetic effects of cannabinoids have been shown across a wide variety of experimental models.[78] CB1 agonists consistently suppress vomiting, while emesis is achieved

through CB1 antagonism. CBD has been shown to exert anti-nausea/anti-emetic effects by indirect agonism of 5-HT1A receptors.[79]

Cardiometabolic Function

The ECS influences metabolic functions, centrally and peripherally, in tissues of the cardiovascular system, GI tract, musculoskeletal system, and other systems as well as in hepatocytes, adipocytes, and other cells.[80] Alterations in endocannabinoid receptors and ligands are found in a number of cardiometabolic diseases, including cardiovascular disease, hypertension, obesity, and diabetes.[81] Individuals with obstructive sleep apnea and diabetes, for example, have been shown to have higher circulating levels of endocannabinoids as compared to controls.[81] Anandamide has also been positively associated with increased blood pressure,[81] while 2-AG has been inversely associated with insulin sensitivity, even after controlling for body fat percentage.[82] In addition, 2-AG has been positively associated with body fat and visceral obesity.[82] In congestive heart failure, for example, human myocardial cells display upregulated CB2 receptors and downregulated CB1 receptors.[83] It's more likely that these associations and alternations are the result of homeostatic reactions to the stresses of cardiometabolic disease than the primary cause of it.

Food Intake and Reward

Cannabinoids can be putatively included in the large family of orexogenic molecules, which are molecules that stimulate appetite.[84] Administration of anandamide has been shown to stimulate appetite in mice.[84] The ECS modulates food intake both centrally and at the level of the GI tract through multiple mechanisms. CB1 receptors are expressed in key hypothalamic systems.[85] Between meals, endocannabinoids gradually increase over time until they reach levels that trigger ECS circuits, thus increasing the motivation to feed.[86]

The dopaminergic system represents one of the most important reward pathways. Cannabinoid-dopaminergic interactions appear to influence feeding behavior.[87,88] Interestingly, the hormone leptin strongly modulates endocannabinoid levels in the hypothalamus.[89] Recent studies have indicated that the regulation of food intake may be affected by genetic impairment of the ECS.[85]

Hypothalamus and HPA Axis

Studies of the endocannabinoid system support its importance in modulation of the hypothalamic-pituitary-adrenal (HPA) axis, including regulation of mood and anxiety and extinction of fear learning.[90] Cannabinoid action on neuroendocrine functioning, including ACTH levels, is mediated by CB1 signaling in the hypothalamus.[91] Alternately, pretreatment with the CB1 antagonist Rimonabant, prior to a stressor, has been shown to blunt HPA function in a mouse model.[91]

Pain and Inflammation

Cannabinoid receptors are present on nociceptors and other sensory neurons in pain processing pathways in the brain and spinal cord,[92] often co-localized with opioid receptors.[27,33] Activation of CB1 receptors in these areas has been shown to inhibit transmission of pain signals to higher brain regions[92] and modulate pain signals in descending pain pathways.[33]

Numerous preclinical studies have demonstrated the beneficial effects of cannabinoids, including CBD, in animal models of acute pain,[93,94] chronic pain, and neuropathic pain,[95,96] some demonstrating opioid-sparing effects. Human studies investigating CBD-induced analgesia in humans, however, are few.[97,98]

The Circadian Sleep–wake Cycle

The ECS has the capacity to modulate circadian rhythms and is involved in the regulation of circadian sleep–wake cycles.[58] Plasma concentrations of anandamide exhibit a circadian rhythm, which can be disrupted by sleep deprivation.[99]

Reproductive System and Embryogenesis

Endocannabinoids are involved in local and central regulation of reproduction and are present in most reproductive fluids and tissues.[100] A properly functioning ECS orchestrates nearly all reproductive events from gamete production and fertilization to successful pregnancy, birth, and lactation. These include proper sperm function,[101] fertilization,[102,103] blastocyst formation,[104] oviduct transport,[105,106] uterine receptivity (decidualization),[107] trophoblast maturation,[108] placental development,[109] and parturition.[110] Interestingly, pharmacologic antagonism of CB1 blocks ECS signaling and leads to failure of pregnancy.[111,112] High levels of maternal anandamide appear detrimental to placental and fetal development. The enzymatic degradation of anandamide appears to be an early marker of spontaneous abortion and may even be useful as a diagnostic tool for monitoring of early pregnancy.[113]

THE ENTOURAGE EFFECT

In popular culture, *the Entourage Effect* has become the preferred phrase for describing the purported physiological synergies engendered by various constituents within the *Cannabis* plant. This effect isn't exclusive to *Cannabis spp.,* however, nor is it exclusive to phytocannabinoids.[114-116]

In fact, the concept originally described interactions between endocannabinoids, specifically the role of 2 endocannabinoid-like mediators—2-acyl-glycerol esters—in increasing the biological activity of 2-AG at the CB1 receptor.[4,117] Additional research has demonstrated that these endocannabinoid-like mediators, with no affinity for the CB1 receptor, also inhibit anandamide metabolism, thus potentially leading to increased levels and greater anandamide signaling.[118]

These examples underscore the important notion that *the Entourage Effect* can exist in the absence of phytocannabinoids. Therefore, perhaps a more accurate

characterization of this phenomenon might describe the sum-total of the pharmacokinetic and pharmacodynamic interactions within and between endocannabinoids and biologically active constituents within *Cannabis*, including terpenes and terpenoids.

Allosteric Modulation

Phytocannabinoids are also involved in pharmacodynamic interactions at the CB1 receptor. For example, CBD has been shown to antagonize delta-9-THC at CB1, presumably through negative allosteric modulation.[119,120] In contrast to ligands that bind to an active site on a receptor—the orthosteric site, allosteric modulators bind to a nonactive site—the allosteric site.

Allosteric modulators can prime receptors for potentiation or antagonism in subtle, yet powerful ways by changing the conformation of a receptor and influencing agonist signaling. Thus, CB1 signaling by delta-9-THC is altered by the presence of CBD. This is one of the ways in which CBD may attenuate some of the undesirable effects of delta-9-THC, such as anxiety, tachycardia, and short-term memory loss.[121] This pharmacodynamic interaction involves 2 phytocannabinoids, just as the aforementioned interaction involved 2, or more, endocannabinoids. CBD may also act as a negative allosteric modulator of 2-AG.[119]

CBD and Non-Cannabinoid Receptors

Allosteric modulators, like CBD, don't activate receptors directly. Thus CBD's widespread biological effects are largely attributable to other mechanisms, including interactions with non-cannabinoid receptors.[3,42,122] CBD is pleiotropic in that it interacts with opioid, serotonin, adenosine, and GABA receptors as well as non-GPCRs-like nuclear receptors, such as PPARγ, and ligand-gated ion channels, such as TRPV1.[123] For example, one of the ways that CBD is thought to modulate inflammation and temperature and pain perception is through activation of TRPV1.[42] Anti-anxiety and anti-emetic effects have been associated with direct and indirect agonism of the 5-HT1A receptor, respectively.[79,124] Anti-proliferative effects, inducing tumor regression, have been associated with PPARs. Please note: This list isn't intended to be comprehensive.[55]

Other indirect mechanisms involving receptors are postulated. For example, CBD may also affect intracellular signal transduction by disturbing neuronal membrane fluidity,[4,125,126] or by remodeling G-proteins associated with GPCRs.[127]

Inhibition of FAAH

Receptor-independent mechanisms have also been demonstrated. Interactions between phytocannabinoids and intracellular enzymes may lead to inhibition of the enzymatic hydrolysis of endocannabinoids, thus increasing their signaling.[117,128] CBD, in particular, has been shown to moderately inhibit anandamide hydrolysis by FAAH in both mice and humans.[3,129-131] Other research suggests that CBD doesn't inhibit human FAAH.[19] Nonsteroidal anti-inflammatory drugs (NSAIDs) are also demonstrated FAAH inhibitors.[95]

Inhibition of FABPs

Other intracellular proteins are also involved in *Entourage* interactions. For example, a family of intracellular transport proteins, FABPs, effectively solubilizes cannabinoids and shuttles them from the cell membrane to the endoplasmic reticulum where they are degraded by FAAH and MAGL in the case of anandamide and 2-AG, respectively. Studies have demonstrated that delta-9-THC and CBD compete with anandamide for binding sites on FABPs, inhibiting the cellular uptake and catabolism of anandamide.[19] In addition to FAAH inhibition, this competition may explain the increased circulating levels of anandamide reported after ingestion of CBD.[132] This mechanism may also explain in part the action of CBD in modulating endocannabinoid tone and its effectiveness in treating epilepsy and other neurological disorders.[133]

CBD, Pain, and Inflammation

The mechanisms underlying CBD-induced analgesia aren't well understood. Inhibition of FAAH and MAGL has been associated with increased endocannabinoid levels, analgesia, and opioid-sparing effects in preclinical models of pain.[134] Broadly speaking, cannabinoids are powerful modulators of inflammatory mediators.[30,31,135] For example, inhibition of tumor necrosis factor-alpha (TNF-α) and other inflammatory mediators by CBD has been demonstrated in a rodent model of acute pain[136] and in another of rheumatoid arthritis.[137] Enhancement of adenosine signaling by CBD through inhibition of adenosine uptake has been associated with decreased inflammation in preclinical models.[138] Additionally, activation of TRPV1 has been shown to inhibit hyperalgesia in an animal model of acute pain.[42] These mechanisms aren't intended to represent an exhaustive list. Cannabinoid-induced analgesia is likely achieved through a complex interplay of mechanisms.

Clinical Endocannabinoid Deficiency (CECD)

In 2004, CECD was coined by neurologist Ethan Russo to describe the potential pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions that seemed to be alleviated by *Cannabis*.[139] Russo hypothesized that a wide variety of medical conditions with previously uncharacterized clinical, biochemical, and pathophysiological features may, in fact, be due to deficiencies, or alterations, in the endocannabinoid system. In 2016, Russo expanded the list of conditions thought to be associated with CECD to include autoimmune disorders, epilepsy, cardiovascular disease, anxiety, depression, failure to thrive, schizophrenia, multiple sclerosis, Parkinson's disease, and others.[140]

Tolerability and Safety of CBD

Comprehensive reviews of the safety and adverse effects of CBD conducted in 2011 and 2017 showed that even chronic use at very high doses—up to 1,500 mg/day of isolated CBD—are safe and well tolerated without significant adverse effects.[141,142] CBD doesn't appear to induce catalepsy nor alter psychomotor and cognitive functions. In addition, the World Health Organization's Expert Committee on Drug Dependence recommended that CBD shouldn't be controlled by Schedule I of the 1961 UN Single Convention on Narcotic Drugs.[143] Their comprehensive report is expected in 2019.

CBD isn't without adverse effects, however. The most commonly reported adverse effects are fatigue, diarrhea, dry mouth, and changes of appetite and weight.[142,144]

When used to treat medical conditions, CBD has a better adverse-effect profile than many FDA-approved drugs.[142] This low-adverse-effect profile can improve patients' adherence to treatment.

It's important to note that the pharmacokinetics and pharmacodynamics of phytocannabinoids may be different across different methods of administration and when administered as components of a botanical extract as opposed to isolated compounds. For example, recent studies show a linear dose-response curve for CBD administered in a broad-spectrum extract and a bell-shaped dose-response curve for CBD administered as an isolated compound.[136] Not only do these differing characteristics influence the dose-response curve, they also influence the adverse-effect profile. The higher efficiency of a plant extract might be explained by additive or synergistic interactions between CBD and other phytocannabinoids or non-cannabinoids present in extracts, the *Entourage Effect*.

CONCLUSIONS

The endocannabinoid system (ECS) is an extensive endogenous signaling system, and its very concept may be changing as scientists continue to elucidate its role in human health and disease. The ECS is seemingly ubiquitous in animal species and modulated by diet, sleep, exercise, stress, and a multitude of other factors, including exposure to phytocannabinoids, like CBD and others. Modulating the activity of this system may offer tremendous therapeutic promise for a diverse scope of diseases, ranging from mental health disorders, neurological and movement disorders, pain, autoimmune disease, spinal cord injury, cancer, cardiometabolic disease, stroke, TBI, osteoporosis, and others.

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