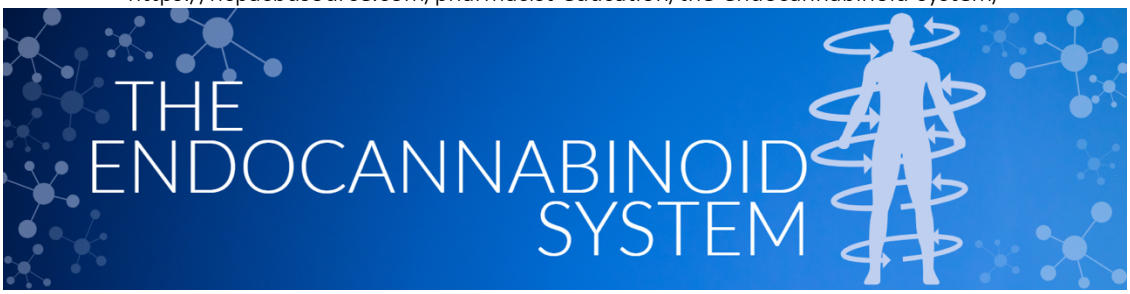
https://ncpacbdsource.com/pharmacist-education/the-endocannabinoid-system/



The human body is enormously complex, and even after doubling human life expectancy in a mere century, the medical and scientific communities have barely scratched the surface of how our minds and bodies really work. The recent and ongoing discovery of the endocannabinoid system has opened the door to the underlying mechanisms of observable phenomena that even Freud predicted but could not identify.

The most other signaling systems, endocannabinoid system comprises three essential parts:

- several Gi/o protein-coupled receptors;
- their endogenous arachidonoyl ligands;
- enzymes which synthesize and degrade those ligands.

The receptors of the endocannabinoid system are the most abundant protein receptors in the human body – more numerous than *all other protein receptors – dopamine, serotonin, GABA, glutamate, etc. –* ***combined.***

58% of transmembrane receptors in the brain are CB1 cannabinoid receptors.

This ubiquitous and pervasive system plays a key role in many nervous system functions, regulating:

- Pleasure;
- Memory;
- Cognition;
- Mood;
- Neural Plasticity;
- Concentration;
- Motor Activity;
- Awareness of Time;
- Appetite;
- Pain Threshold and Perception;
- Integration of the Senses.

It also plays several roles in the immune system:

- cell differentiation and activation;
- gene transcription;
- anti- and pro-inflammatory cascades;
- cellular chemotaxis.

The two most well known endocannabinoids are **arachidonylethanolamide (AEA)** – *more commonly known as* ***anandamide*** – and **2-arachidonoylglycerol (2-AG).**

Not long after Δ9-THC was first isolated from the cannabis plant by Rafael Mechoulam, scientists realized that the human body had a unique and as-yet undiscovered receptor upon which THC exerted its psychoactive effects.

As the science of the endocannabinoid system progressed, its true roles have slowly but surely bubbled to the surface, and answered many questions that have baffled the healthcare community since antiquity, from the role of dreams and memory consolidation, to how inflammation really works.

This article outlines some of the more well-understood endocannabinoids, cannabinoid receptors, and the role of the endocannabinoid system as it relates to health and disease.

So, maintaining a healthy endocannabinoid system means maintaining a healthy lifestyle. Benefits of optimizing your endocannabinoid system may include:

- Relieving depression
- Increasing myelin (protective layer around your nerves) formation
- Lowering intestinal inflammation
- Decreasing intestinal permeability (Leaky Gut Syndrome)
- Lowering blood pressure
- Lowering anxiety
- Reducing paranoia

The endocannabinoid system is highly impactful and complex but relies largely on a few key endocannabinoids and receptors to function properly.

What Are Endocannabinoids?

Endogenous cannabinoids, or endocannabinoids, are neurotransmitters naturally produced by the body. They bind to cannabinoid receptors, specifically CB1 and CB2 receptors, located throughout the brain, immune system, and elsewhere. Examples include anandamide, 2-arachidonoylglycerol (2-AG), n-arachidonoyl dopamine (NADA), and virodhamine (OAE).

Endocannabinoids are created and perform in the reverse of more well-known neurotransmitters like serotonin, dopamine, and norepinephrine.

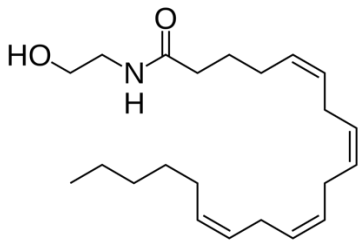
For example, dopamine is produced in advance, stored, and then released from the presynaptic cell in response to stimuli. The dopamine crosses a synapse to reach and activate the postsynaptic cell, which then causes you to feel happy, motivated, and focused. (Dopamine plays a role in several other neurological and motor functions, but is most often associated with your brain's reward system.)

Endocannabinoids, on the other hand, are key components of cellular membranes the body is able to manufacture on demand, not in advance, and they travel backward: endocannabinoids first leave the postsynaptic cell and end their journey in the presynaptic cell. This process allows the postsynaptic cell to regulate the flow of neurotransmitters coming from the presynaptic cell.

While all endocannabinoids play an important role in regulating pre- and postsynaptic activity, one of the best researched is anandamide, perhaps for its reputation as the "bliss molecule."

Anandamide: The Bliss Molecule

Anandamide was first discovered and isolated in the early 1990s and is synthesized in the parts of the brain responsible for memory, motivation, and higher thought processes. Because of its positive effects on mood, it is called the "bliss molecule" (ananda translates to "bliss" in Sanskrit).



Anandamide has been shown to stop cancer cell formation, reduce anxiety and depression, and even increase neurogenesis in patients with Alzheimer's disease. Recently, it has even been proven that anandamide helps produce the 'runner's high' you experience after intense exercise.

A 2015 study by German researchers examined the role of different neurochemicals in creating the runner's high in mice; previously, endorphins were believed to be solely responsible for generating those pronounced post-workout feelings of contentment and happiness. Surprisingly, the researchers found endorphin molecules to be too large to pass the blood-brain barrier, leading them to conclude that the activation of cannabinoid receptors by anandamide is primarily responsible for reducing stress and pain after exercise.

Further studies have found anandamide to play a significant role in babies' and mothers' lives from conception to breastfeeding.

In a 2009 study, researchers found that anandamide levels rose significantly during ovulation in women who would become pregnant via intracytoplasmic sperm injection (ICSI) and in-vitro fertilization (IVF) methods. The study concludes, "Our observations suggest that in successful pregnancy, a higher plasma AEA [anandamide] level at ovulation and a significantly lower level during implantation are required."

A comprehensive review of the roles endocannabinoids play in human reproduction also points to anandamide as being imperative for successful embryo implantation and fetal development. The review states that abnormal function of endocannabinoids or their receptors, especially as they relate to the placenta, could result in pregnancy complications.

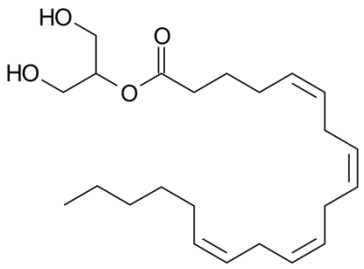
Finally, anandamide, along with the 2-AG endocannabinoid, may be pivotal in triggering a suckling response in newborn babies. A 2006 scientific review found correlations between increased levels of these endocannabinoids and baby mice's ability to latch and suckle. The mice pups naturally had high levels of endocannabinoids within their first day of being born, and as they suckled, their endocannabinoid levels were replenished by the mother's milk. When the mice pups were given a CB1 receptor antagonist, which prevented the CB1 receptor from being activated by anandamide or 2-AG, the newborn mice were not able to suckle.

As you can see, anandamide is important for regular and healthy bodily function. So how can you make sure you have enough of it? A primary building block in the synthesis of anandamide is arachidonic acid (AA), an omega-6 fatty acid found almost exclusively in animal foods (e.g. different meats and eggs), but can also be found in pasta and grain dishes. As long as you are eating a varied and balanced diet, chances are you are getting enough AA to maintain regular anandamide levels.

Interestingly, anandamide is chemically similar to tetrahydrocannabinol (THC), the cannabinoid from the cannabis plant responsible for the 'high' most people associate with consuming marijuana. Because anandamide and THC are similarly structured, they both activate the CB1 receptors with similar potency. However, THC comes with a slew of mind-altering effects, and while it may bring feelings of psychedelic bliss for some, it is no substitute for the bliss molecule.

2-AG: The Real Agonist

Another primary endocannabinoid, 2-arachidonoylglycerol does not receive quite the same amount of attention but has been shown to be present at concentrations 170x greaterthan anandamide in the brain.



Moreover, while anandamide is a selective partial agonist for the CB1 receptor, 2-AG is a full agonist at both the CB1 and CB2 receptors. In other words, 2-AG is much more effective at activating cannabinoid receptors than anandamide.

2-AG is one of the neurotransmitters that play a significant role in the body's immune response. 2-AG was found to exhibit an immunosuppressive effect by causing the body to generate lower levels of cytokines, which are small proteins, produced in immune cells that initiate and promote inflammatory responses in the body.

One of the most celebrated attributes of 2-AG is its neuroprotective effects. In both cases of brain injury and neurodegenerative conditions like Parkinson's Disease, increased amounts of 2-AG were found to protect the brain from further damage.

Like anandamide, 2-AG originates from arachidonic acid but differs in that it is also synthesized using glycerol (also referred to as glycerin). In food, glycerol is often used as a sweetener, filler, and preservation agent. Recently, glycerol has also shown up as a prominent ingredient in e-cigarette vaping liquid.

If you do not have enough of these critical endogenous cannabinoids, it can lead to clinical endocannabinoid deficiency.

CB1 & CB2 Cannabinoid Receptors

Not only do humans produce their own cannabinoids, but they also have cannabinoid receptors designed specifically to recognize and respond to them. These receptors are called CB1 and CB2.

CB1 receptors exist in full numbers on your brain's nerve cells, or neurons, especially those in the hypothalamus, hippocampus, and amygdala, which are primarily responsible for regulating hormones, memory, and emotion, respectively. CB1 receptors are also found in the central nervous system (CNS), intestines, muscles, thyroid gland, and various other organs and glands.

Poorly functioning CB1 receptors can lead to a number of consequences, including:

- Decreased brain energy and function.
- Age-related decline in cognitive faculties
- Irregular hormone production in the thyroid gland, which controls metabolism, digestion, and heart rate.
- Fatty liver disease.
- Irregular food intake.

CB2 receptors (first discovered in 1993) occur most commonly in the spleen, tonsils, thymus, and immune cells; only a small number exist in the brain. CB2 receptors are best known for their role in regulating immune function through their ability to trigger and stop immune responses, including inflammation.

Changes in CB2 receptor function plays a role in human disease; whether cardiovascular, gastrointestinal, neurodegenerative, psychiatric, autoimmune, or cancerous, virtually any ailment of the body or mind is linked to abnormal CB2 function.

Together, the body's endocannabinoids and the CB1 and CB2 receptors that bind with them form the endocannabinoid system.

Clinical Endocannabinoid Deficiency (CECD)

Clinical endocannabinoid deficiency is a condition where an individual has a lower amount of endogenous cannabinoids than considered necessary to live healthily.

Scientists now believe CECD may play a role in the following conditions:

- Fibromyalgia
- Irritable Bowel Syndrome (IBS)
- Migraines
- Multiple Sclerosis (MS)
- Post-Traumatic Stress Disorder (PTSD)
- Neuropathy
- Huntington's disease
- Parkinson's disease
- Motion Sickness
- Autism

Consider for a moment all the medications physicians prescribe on a daily basis for these conditions—and then think of the side effects that can accompany those drugs. For the most part, traditional medications provide some form of relief but also present new issues in the form of unwanted side effects.

If you are suffering from endocannabinoid deficiency, you may be able to improve your condition by making small changes to your diet and/or vitamin and supplement regimen.

Related Conditions:

Neurodegenerative Disorders

Neuroprotective mechanisms promote neurogenesis, and reduce neuro-inflammation and oxidative stress

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Cannabidiol reduces Aβ-induced neuroinflammation and promotes hippocampal neurogenesis through PPARγ involvement.

Esposito G[1], Scuderi C, Valenza M, Togna GI, Latina V, De Filippis D, Cipriano M, Carratù MR, Iuvone T, Steardo L.
Author information

Abstract

Peroxisome proliferator-activated receptor-γ (PPARγ) has been reported to be involved in the etiology of pathological features of Alzheimer's disease (AD). Cannabidiol (CBD), a Cannabis derivative devoid of psychomimetic effects, has attracted much attention because of its promising neuroprotective properties in rat AD models, even though the mechanism responsible for such actions remains unknown. This study was aimed at exploring whether CBD effects could be subordinate to its activity at PPARγ, which has been recently indicated as its putative binding site. CBD actions on β-amyloid-induced neurotoxicity in rat AD models, either in presence or absence of PPAR antagonists were investigated. Results showed that the blockade of PPARγ was able to significantly blunt CBD effects on reactive

gliosis and subsequently on neuronal damage. Moreover, due to its interaction at PPARγ, CBD was observed to stimulate hippocampal neurogenesis. All these findings report the inescapable role of this receptor in mediating CBD actions, here reported.

Osteoarthritis & Rheumatoid Arthritis
Inhibition of the anti-inflammatory cascade and modulation of PPARγ limits the progression of arthritic disease.

Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis.

Philpott HT[1], O'Brien M, McDougall JJ.
Author information

Abstract

Osteoarthritis (OA) is a multifactorial joint disease, which includes joint degeneration, intermittent inflammation, and peripheral neuropathy. Cannabidiol (CBD) is a noneuphoria producing constituent of cannabis that has the potential to relieve pain. The aim of this study was to determine whether CBD is anti-nociceptive in OA, and whether inhibition of inflammation by CBD could prevent the development of OA pain and joint neuropathy. Osteoarthritis was induced in male Wistar rats (150-175 g) by intra-articular injection of sodium monoiodoacetate (MIA; 3 mg). On day 14 (end-stage OA), joint afferent mechanosensitivity was assessed using in vivo electrophysiology, whereas pain behaviour was measured by von Frey hair algesiometry and dynamic incapacitance. To investigate acute joint inflammation, blood flow and leukocyte trafficking were measured on day 1 after MIA. Joint nerve myelination was calculated by G-ratio analysis. The therapeutic and prophylactic effects of peripheral CBD (100-300 μg) were assessed. In end-stage OA, CBD dose-dependently decreased joint afferent firing rate, and increased withdrawal threshold and weight bearing ($P < 0.0001$; $n = 8$). Acute, transient joint inflammation was reduced by local CBD treatment ($P < 0.0001$; $n = 6$). Prophylactic administration of CBD prevented the development of MIA-induced joint pain at later time points ($P < 0.0001$; $n = 8$), and was also found to be neuroprotective ($P < 0.05$; $n = 6$-8). The data presented here indicate that local administration of CBD blocked OA pain. Prophylactic CBD treatment prevented the later development of pain and nerve damage in these OA joints. These findings suggest that CBD may be a safe, useful therapeutic for treating OA joint neuropathic pain.

Depression, Anxiety & PTSD
5-HT1a receptor agonism and induction of endocannabinoid receptors has shown efficacy in several mental health models.

Cannabidiol induces rapid-acting antidepressant-like effects and enhances cortical 5-HT/glutamate neurotransmission: role of 5-HT1A receptors.

Linge R[1], Jiménez-Sánchez L[2], Campa L[2], Pilar-Cuéllar F[1], Vidal R[1], Pazos A[1], Adell A[3], Díaz Á[4].
Author information

Abstract

Cannabidiol (CBD), the main non-psychotomimetic component of marihuana, exhibits anxiolytic-like properties in many behavioural tests, although its potential for treating major depression has been poorly explored. Moreover, the mechanism of action of CBD remains unclear. Herein, we have evaluated the effects of CBD following acute and chronic administration in the olfactory bulbectomy mouse model of depression (OBX), and investigated the underlying mechanism. For this purpose, we conducted behavioural (open field and sucrose preference tests) and neurochemical (microdialysis and autoradiography of 5-HT1A receptor functionality) studies following treatment with CBD. We also assayed the pharmacological antagonism of the effects of CBD to dissect out the mechanism of action. Our

results demonstrate that CBD exerts fast and maintained antidepressant-like effects as evidenced by the reversal of the OBX-induced hyperactivity and anhedonia. In vivo microdialysis revealed that the administration of CBD significantly enhanced serotonin and glutamate levels in vmPFCx in a different manner depending on the emotional state and the duration of the treatment. The potentiating effect upon neurotransmitters levels occurring immediately after the first injection of CBD might underlie the fast antidepressant-like actions in OBX mice. Both antidepressant-like effect and enhanced cortical 5-HT/glutamate neurotransmission induced by CBD were prevented by 5-HT1A receptor blockade. Moreover, adaptive changes in pre- and post-synaptic 5-HT1A receptor functionality were also found after chronic CBD. In conclusion, our findings indicate that CBD could represent a novel fast antidepressant drug, via enhancing both serotonergic and glutamate cortical signalling through a 5-HT1A receptor-dependent mechanism.

Insomnia

Balance within the endocannabinoid system helps maintains a multitude of variables relating to homeostasis and our circadian rhythm.

Effectiveness of Cannabidiol Oil for Pediatric Anxiety and Insomnia as Part of Posttraumatic Stress Disorder: A Case Report.

Shannon S[1], Opila-Lehman J[2].
Author information

Abstract

INTRODUCTION:

Anxiety and sleep disorders are often the result of posttraumatic stress disorder and can contribute to an impaired ability to focus and to demonstration of oppositional behaviors.

CASE PRESENTATION:

These symptoms were present in our patient, a ten-year-old girl who was sexually abused and had minimal parental supervision as a young child under the age of five. Pharmaceutical medications provided partial relief, but results were not long-lasting, and there were major side effects. A trial of cannabidiol oil resulted in a maintained decrease in anxiety and a steady improvement in the quality and quantity of the patient's sleep.

DISCUSSION:

Cannabidiol oil, an increasingly popular treatment of anxiety and sleep issues, has been documented as being an effective alternative to pharmaceutical medications. This case study provides clinical data that support the use of cannabidiol oil as a safe treatment for reducing anxiety and improving sleep in a young girl with posttraumatic stress disorder.

Side Effects of Chemotherapy

Chemotherapy harms good cells as well as bad cells. Endocannabinoid regulation protects healthy cells and promotes apoptosis of diseased cells.

Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT(1A) receptors without diminishing nervous system function or chemotherapy efficacy.

Ward SJ[1], McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA.
Author information

Abstract

BACKGROUND AND PURPOSE:

Paclitaxel (PAC) is associated with chemotherapy-induced neuropathic pain (CIPN) that can lead to the cessation of treatment in cancer patients even in the absence of alternate therapies. We previously reported that chronic administration of the non-psychoactive

cannabinoid cannabidiol (CBD) prevents PAC-induced mechanical and thermal sensitivity in mice. Hence, we sought to determine receptor mechanisms by which CBD inhibits CIPN and whether CBD negatively effects nervous system function or chemotherapy efficacy.

EXPERIMENTAL APPROACH:

The ability of acute CBD pretreatment to prevent PAC-induced mechanical sensitivity was assessed, as was the effect of CBD on place conditioning and on an operant-conditioned learning and memory task. The potential interaction of CBD and PAC on breast cancer cell viability was determined using the MTT assay.

KEY RESULTS:

PAC-induced mechanical sensitivity was prevented by administration of CBD (2.5 - 10 $mg \cdot kg^{-1}$) in female C57Bl/6 mice. This effect was reversed by co-administration of the 5-HT(1A) antagonist WAY 100635, but not the CB_1 antagonist SR141716 or the CB_2 antagonist SR144528. CBD produced no conditioned rewarding effects and did not affect conditioned learning and memory. Also, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability.

CONCLUSIONS AND IMPLICATIONS:

Our data suggest that CBD is protective against PAC-induced neurotoxicity mediated in part by the 5-HT(1A) receptor system. Furthermore, CBD treatment was devoid of conditioned rewarding effects or cognitive impairment and did not attenuate PAC-induced inhibition of breast cancer cell viability. Hence, adjunct treatment with CBD during PAC chemotherapy may be safe and effective in the prevention or attenuation of CIPN.

Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes.

Oláh A, Tóth BI, Borbíró I, Sugawara K, Szöllõsi AG, Czifra G, Pál B, Ambrus L, Kloepper J, Camera E, Ludovici M, Picardo M, Voets T, Zouboulis CC, Paus R, Bíró T.

Abstract

The endocannabinoid system (ECS) regulates multiple physiological processes, including cutaneous cell growth and differentiation. Here, we explored the effects of the major nonpsychotropic phytocannabinoid of Cannabis sativa, (-)-cannabidiol (CBD), on human sebaceous gland function and determined that CBD behaves as a highly effective sebostatic agent. Administration of CBD to cultured human sebocytes and human skin organ culture inhibited the lipogenic actions of various compounds, including arachidonic acid and a combination of linoleic acid and testosterone, and suppressed sebocyte proliferation via the activation of transient receptor potential vanilloid-4 (TRPV4) ion channels. Activation of TRPV4 interfered with the prolipogenic ERK1/2 MAPK pathway and resulted in the downregulation of nuclear receptor interacting protein-1 (NRIP1), which influences glucose and lipid metabolism, thereby inhibiting sebocyte lipogenesis. CBD also exerted complex antiinflammatory actions that were coupled to A2a adenosine receptor-dependent upregulation of tribbles homolog 3 (TRIB3) and inhibition of the NF-κB signaling. Collectively, our findings suggest that, due to the combined lipostatic, antiproliferative, and antiinflammatory effects, CBD has potential as a promising therapeutic agent for the treatment of acne vulgaris.

Acute & Chronic Inflammation

PPARγ receptor modulation reduces proinflammatory markers and lymphocyte activation, while inhibition of COX enzymes limits prostaglandin production.

Cannabinoids as novel anti-inflammatory drugs

Prakash Nagarkatti,[†] Rupal Pandey,[*] Sadiye Amcaoglu Rieder,[*] Venkatesh L Hegde, and Mitzi Nagarkatti

Abstract

Cannabinoids are a group of compounds that mediate their effects through cannabinoid receptors. The discovery of Δ^9-tetrahydrocannabinol (THC) as the major psychoactive principle in marijuana, as well as the identification of cannabinoid receptors and their endogenous ligands, has led to a significant growth in research aimed at understanding the physiological functions of cannabinoids. Cannabinoid receptors include CB1, which is predominantly expressed in the brain, and CB2, which is primarily found on the cells of the immune system. The fact that both CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Recent studies demonstrated that administration of THC into mice triggered marked apoptosis in T cells and dendritic cells, resulting in immunosuppression. In addition, several studies showed that cannabinoids downregulate cytokine and chemokine production and, in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses. The endocannabinoid system is also involved in immunoregulation. For example, administration of endocannabinoids or use of inhibitors of enzymes that break down the endocannabinoids, led to immunosuppression and recovery from immune-mediated injury to organs such as the liver. Manipulation of endocannabinoids and/or use of exogenous cannabinoids *in vivo* can constitute a potent treatment modality against inflammatory disorders. This review will focus on the potential use of cannabinoids as a new class of anti-inflammatory agents against a number of inflammatory and autoimmune diseases that are primarily triggered by activated T cells or other cellular immune components.

Epilepsy & Seizure Disorders

Endocannabinoid activity reduces seizure frequency and excess excitability by stabilizing glutamatergic and GABAergic signaling.

Cannabidiol Displays Antiepileptiform and Antiseizure Properties In Vitro and In Vivo

Nicholas A. Jones, Andrew J. Hill, Imogen Smith, Sarah A. Bevan, Claire M. Williams, Benjamin J. Whalley, and Gary J. Stephens

Abstract

Plant-derived cannabinoids (phytocannabinoids) are compounds with emerging therapeutic potential. Early studies suggested that cannabidiol (CBD) has anticonvulsant properties in animal models and reduced seizure frequency in limited human trials. Here, we examine the antiepileptiform and antiseizure potential of CBD using in vitro electrophysiology and an in vivo animal seizure model, respectively. CBD (0.01–100 μM) effects were assessed in vitro using the Mg^{2+}-free and 4-aminopyridine (4-AP) models of epileptiform activity in hippocampal brain slices via multielectrode array recordings. In the Mg^{2+}-free model, CBD decreased epileptiform local field potential (LFP) burst amplitude [in CA1 and dentate gyrus (DG) regions] and burst duration (in all regions) and increased burst frequency (in all regions). In the 4-AP model, CBD decreased LFP burst amplitude (in CA1 only at 100 μM CBD), burst duration (in CA3 and DG), and burst frequency (in all regions). CBD (1, 10, and 100 mg/kg) effects were also examined in vivo using the pentylenetetrazole model of generalized seizures. CBD (100 mg/kg) exerted clear anticonvulsant effects with significant decreases in incidence of severe seizures and mortality compared with vehicle-treated animals. Finally, CBD acted with only low affinity at cannabinoid CB_1 receptors and displayed no agonist activity in [^{35}S]guanosine 5′-*O*-(3-thio)triphosphate assays in cortical membranes. These findings suggest that CBD acts, potentially in a CB_1 receptor-independent manner, to inhibit epileptiform activity in vitro and seizure severity in vivo. Thus, we demonstrate the potential of CBD as a novel antiepileptic drug in the unmet clinical need associated with generalized seizures.

Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5-HT_{1A} receptors without diminishing nervous system function or chemotherapy efficacy

Sara Jane Ward,[1] Sean D McAllister,[2] Rumi Kawamura,[2] Ryuchi Murase,[2] Harshini Neelakantan,[3] and Ellen A Walker[3]

Abstract

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Keywords: cannabidiol, paclitaxel, chemotherapy-induced neuropathic pain, CIPN, 5-HT_{1A}, breast cancer, cannabinoid, mechanical sensitivity