Contents

CBD IS AN ESSENTIAL NUTRIENT MOST OF US LACK ................................................................. 8
THE HISTORY OF CANNABIS .......................................................................................................... 8
THE ENDOCANNABINOID SYSTEM ............................................................................................... 9
CBD oil is an ESSENTIAL NUTRIENT NOT a PHARMACEUTICAL DRUG .................................... 10
Kannaway Pure Gold is the First CBD Product to be Included in Prescribers' Digital Reference ADVERT ................................................................. 11

Cannabinoid receptors: where they are and what they do .......................................................... 13
CBD studies with the greatest impact over the past year ............................................................. 14
Table of Contents .......................................................................................................................... 14
CBD Research Round-Up .............................................................................................................. 14
Overarching Conclusions ............................................................................................................. 15
CBD and Treatment-Resistant Seizures ........................................................................................ 15
An Explanation of Epilepsy ............................................................................................................. 16
Study Parameters and Results ........................................................................................................ 16
Seizures in Children and How CBD Therapy Might Help ............................................................ 17
Trial Parameters and Process ......................................................................................................... 17
Results ........................................................................................................................................... 18
Can CBD Help Manage Fear? ........................................................................................................ 18
Afraid of Public-Speaking? CBD Might Help .............................................................................. 19
Results ........................................................................................................................................... 20
Potential Anti-panic Actions of CBD ............................................................................................ 21
Does CBD Reduce High Blood Pressure? .................................................................................... 21
Does CBD Get You High? .............................................................................................................. 22
The Prior Studies .......................................................................................................................... 23
The Misinterpretations .................................................................................................................. 23
CBD Doesn’t Make You Burn Through a Box of Oreos ............................................................... 24
CBD’s Potential Lack of Effect on Anxiety .................................................................................. 25
Study Parameters .......................................................................................................................... 26
The Impact ....................................................................................................................................... 26
CBD’s Relevance to Schizophrenia .............................................................................................. 27
Cannabis vs. Opioid-Based Pain Medication: Patient Self-Report ................................................................. 28
CBD and Opioid Use: First Long Term Study .................................................................................................. 28
CBD and Irritable Bowel Disease .................................................................................................................. 29
Liver Injury and CBD’s Potential Healing Effect ............................................................................................. 30
A Potential Aid in Brain Recovery After a Stroke ........................................................................................... 31
Pain and CBD’s Potential Effect ..................................................................................................................... 32
What’s Next? …........................................................................................................................................ 33
Short-Term Efficacy of CBD-Enriched Hemp Oil in Girls with Dysautonomic Syndrome after Human Papillomavirus Vaccination ........................................................................................................ 34
Abstract ...................................................................................................................................................... 35
1. Introduction............................................................................................................................................ 35
2. Cannabinoid Receptors ............................................................................................................................. 36
3. Endocannabinoid System .......................................................................................................................... 37
4. Endocannabinoid-Mediated Signaling ....................................................................................................... 37
5. Distribution of Cannabinoid Receptors ...................................................................................................... 40
6. Cannabinoid Receptor Signaling ............................................................................................................. 43
7. Physiological and Pathological Roles of the CB1R ......................................................................................... 46
8. Future Directions of Cannabinoid-Based Drug Discovery .......................................................................... 50
9. Conclusions............................................................................................................................................. 51
Acknowledgments ........................................................................................................................................ 52
Abbreviations .............................................................................................................................................. 52
Author Contributions ................................................................................................................................... 56
Conflicts of Interest ....................................................................................................................................... 57
References ..................................................................................................................................................... 57
The Vitamin effect versus The Drug effect

Vitamins allow Action, Drugs Demand action. A balance of Vitamins is needed for health, natural wellness and harmonious homeostasis. Natural and organic vitamins are all part of a balanced world. Synthetic made vitamins are not the same as natural. Similar maybe, but definitely not the same. So synthetic vitamins will upset all natural process. To use synthetic anything is an INSULT to the Body.

This issue of the journal will focus on CBD oil as a nutrient.

Drugs will stimulate or depress natural processes to treat a symptom but in so doing will upset natural balance and thus produce side effects that often build into other diseases. Most drugs are synthetically made and are not part of the balance of nature. A patent by definition means it is un-natural, thus synthetic.

Vitamins are substances that your body needs to grow, metabolize, reproduce and develop normally. Vitamins can supply needed nutrients or collective complex nutrient support compounds. Vitamins can act like enzymes or to assist enzymes in minimizing the energy needed make compounds or to balance metabolism. A balance of Vitamins is needed for all factors of life. Too little or Too Much of any Vitamin can upset the balance and produce disease.

A vitamin is an organic molecule (or related set of molecules) that is an essential micronutrient that an organism needs in small quantities for the proper functioning of its metabolism. Essential nutrients cannot be synthesized in the organism, either at all or not in sufficient quantities, and therefore must be obtained through the diet. Vitamin C can be produced by some species but not by others; it is not a vitamin in the first instance but is in the second. The term vitamin does not include the three other groups of essential nutrients: minerals, essential fatty acids, and essential amino acids.

Foods are our Best Medicine. Foods should supply our vitamins. However, soil depletion, bad diet, food processing, even cooking deplete vitamins. Everyone has different vitamin needs and disease can change our needs as well. So vitamin
therapy is needed for medicine. And we should not always expect immediate results from supplying the correct nutrients.

When it comes to vitamins we need to specify whether it is essential for life vs essential for health, or essential for peak performance.

Modern Chemical Medicine calls itself heroic medicine or Crisis Care, as it saves you from the jaws of death. Meaning they wait till the last moment to give you a synthetic pill or surgery. Essential for the Allopathic Medical doctor means essential for life; if you do not get it, you die.

The Natural medicine is preventative medicine and thus Essential means essential for health and preventing disease.

Natural Sports Performance medicine strives for Peak Performance and wants minimal side effects.

SINthetic Pharmaceutical drugs mask important axillary symptoms while only treating the major presenting symptom; they don’t get to the root cause of the medical problem. Nobody is ever sick because they are deficient of a SINthetic drug. But SINthetic Pharmaceutical drugs usually provide instant gratification by demanding action. People like instant results even if there are disease complications in the future. Instant rewards outweigh long term consequences for the small minded.

In acute situations, SINthetic drugs can save your life. In addition, sometimes they are helpful and necessary. But when an entire population has been falsely led to believe that finding and taking the right drug for every ill is the “Magic Bullet” of healthcare, we have a problem. The drive for competitive profit over people in the drug industry will greatly oppose and attack NON-Drug therapies like CBD oil.

Most health conditions respond so beautifully to holistic treatments. Meanwhile, every now and then, our attention is very cleverly turned away from the treatments we’re led to trust without question (drugs) in order to stop us from doing the things that actually contribute to health—like taking vitamins.

In 2010, drug-related deaths were the number one cause of injury deaths in the U.S., according to the Centers for Disease Control and Prevention (CDC)? Here are just a few facts from the CDC’s findings:
• Approximately 9 out of 10 poisoning deaths are caused by prescription and over-the-counter drugs.

• In 2010, there were 38,329 deaths from drug overdose (an injury death). However, 78% of all individuals (30,006) did not intentionally overdose, and 60% (22,134) of these cases were related to pharmaceutical drugs. Included in the 60% are people who took their medication as directed by their doctor.

• In 2011, 2.5 million individuals were treated in the emergency room for drug abuse or misuse (taking it differently than the way it was prescribed). More than half—1.4 million emergency room visits—were related to prescribed or over-the-counter medicine.

In absolute stark contrast, there were no deaths from vitamin, mineral, or other herbal or nutritional supplements in 2010. Not even one! We know this from the U.S. National Poison Data Systems’ report. None of the 57 Poison Control Centers across the U.S. reported any deaths from nutritional supplements. It’s shocking to learn that about 80% of deaths reported by U.S. Poison Control Centers were the result of taking a prescription or over-the-counter medication—both of which are regulated and approved by the FDA. And that includes acetaminophen, the ingredient in Tylenol and many other products. Regarding acetaminophen alone, there are 100,000 calls to Poison Control, 56,000 visits to the emergency room, 2,600 hospital admissions, and nearly 500 deaths per year! If you are wondering about side effects from vitamins, minerals, and other supplements versus side effects from medication, nutritional supplements come out on top again. One of the measures enacted by Congress to monitor the nutritional supplement industry is the FDA’s Adverse Effects Reporting (AER) protocol. Here are some stats released in the March 2013 GAO Dietary Supplements report on data from 2008:

• 1,080 AERs on supplements were reported
• 526,527 AERs on prescription drugs were reported

And this is for one year! Yes—I realize that there are all kinds of negative studies in the news about this supplement or that supplement. Many were poorly designed or report on skewed data, just like my example. Besides, treating nutrients like drugs—and holding them to the same standards as drugs—is
Nutritional supplement safety in 2010 is no different today. And the industry has enjoyed similar if not identical safety levels for the last 25 or more years. That’s not to say that there isn’t a quality difference between brands. There is! So choose a high-quality supplement from a manufacturer you trust. You can also expect the same concerns to continue from pharmaceutical and some over-the-counter medications. So be careful and be informed! What is your experience with prescription or over-the-counter medications? What advice would you give to someone who is concerned about the safety of nutritional supplements?

References:


Understanding how cannabinoids have been a vital part of our diet for thousands of years could point towards long-term damage as a result of its removal from livestock in the 30’s.

CBD’s prevalence in the health foods market seems to be facing a momentous surge in popularity. With many claiming it has helped them both mentally and physically, the demand has risen sharply. Already backed by many health professionals, the calling for even more detailed research continues. It seems almost everyone wants in on the action.

Could the desire for CBD actually be the result of a wholesale removal of cannabinoids from our diet, starving ourselves of nutrients we used to receive? In turn, driving a rise in our susceptibility to diseases and illness? Increasingly, doctors and medical professionals believe that nutrient deficiency could be a direct cause of these conditions. If you then consider CBD for its nutritional value to our body, it should be viewed, NOT as a pharmaceutical drug, but CBD is an essential natural health food.

What Is Clinical Endocannabinoid Deficiency?

THE HISTORY OF CANNABIS

We consider cannabis to be fairly new in terms of our understanding of its properties. However, recent discoveries point to the use of cannabis as a medicinal aid dating back thousands of years. In 2016, Chinese
archaeologists uncovered a 2,500-year-old burial site. What they found was none other than, you guessed it, cannabis. From the remains found they were able to deduce, that the cannabis was locally harvested, with the flowering tops having been removed. Furthermore in another site close by powdered leaves and cannabis seeds were found. Clearly, the medicinal and psychoactive properties of this now stigmatized plant were being freely used.

If we fast forward a bit in time, it wasn't until after 1937, that hemp was removed from feed for our livestock. Prior to this, the phytocannabinoids found in hemp were in the majority of our food supply. Integration through livestock as a result of their feed, including pigs, chicken, and general cattle. The reason hemp was used was for its high protein and amino acids. From there it naturally became part of all of our diet. Consuming meat and milk from the animals passed these phytocannabinoids onto us, absorbing them through our digestion system and interacting with our endocannabinoid system.

THE ENDOCANNABINOID SYSTEM

Given that at one point in time our endocannabinoid system was being supplemented by our diets, what is the endocannabinoid system responsible for? Present in all mammals, it is a collection of cannabinoid receptors located throughout the brain and central nervous system. Linked to a number of physiological effects like appetite, pain relief, mood and memory, the manipulation of said receptors has seen some very beneficial results in preliminary research. Whilst our body produces its own endocannabinoids, these receptors can be stimulated by the presence of the cannabinoids within cannabis and hemp.
CBD oil is an ESSENTIAL NUTRIENT NOT a PHARMACEUTICAL DRUG

The debate for this rages on, with opinions reaching an all-time high, largely driven by the increasing amount of research being conducted into CBD and cannabinoids other than THC. It is the THC, that gives cannabis its illegal nature classing it as a drug. THC is largely responsible for the psychoactive properties that users experience when smoking cannabis. However, heating the cannabis through smoking or cooking is required to create the THC. If you consume cannabis raw, these properties have yet to be activated. You instead receive an entirely different set of cannabinoids. Hemp is an easy way of receiving these cannabinoids.

Nutrients are a vital part of a functioning cell, without them, many bodily functions would simply not work. If by consuming hemp rich in otherwise missed compounds, does it not then become a health food? Despite the psychoactive aspects associated with cannabis, it is only one part of the plant's complex genetics. One thing is certain, regardless of your view, further research is required to fully understand how we can benefit from cannabis in all its forms.
Kannaway’s Pure Gold became the first CBD product to ever be included among the prescribing guidelines provided in the U.S. Prescribers’ Digital Reference when the product was added to the 2019 edition of the important healthcare resource.

The Prescribers’ Digital Reference or “PDR” (known in its physical form as the Physicians’ Desk Reference) delivers comprehensive and innovative knowledge on the health industry’s products and services to support the prescribing decisions of health professionals.

This inclusion of Kannaway’s Pure Gold in the PDR is an important milestone for CBD as it gains acceptance by the medical community as a health and wellness compound. The information regarding CBD in the publication normalizes its use in modern medicine and encourages dialogue regarding CBD. You can find the entry in the Prescribers’ Digital Reference for Pure Gold [here](https://www.pdr.net/). A common term when researching CBD oil products is “entourage effect” – referring to the potential multiplying of effects that is theorized to take place when full-spectrum cannabis oil is used. The term entourage effect was first introduced in cannabinoid science in 1998 by S. Ben-Shabat, along with noted cannabis researcher Raphael Mechoulam, to represent a potential enhancing effect that takes place when a full-spectrum of cannabinoids and terpenoids is consumed.

In discussing this new theory, the researchers stated, “This type of synergism may play a role in the widely held (but not experimentally based) view that in some cases plants are better drugs than the natural products isolated from them.” While CBD, along with THC, has become a major topic in the therapeutic use of cannabis products, the idea that other cannabinoids and terpenoids may also contribute to CBD oil’s beneficial effects has been coined as the entourage effect.
Besides the major cannabinoids (THC and CBD), cannabis oils derived from different hemp and marijuana plants may also contain minor trace cannabinoids – like tetrahydrocannabivarin (THCV), cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), and cannabidiolic acid (CBDA) to name just a few of the over 100 cannabinoids present in cannabis.

While many of these cannabinoids possess individual benefits, the theory of the entourage effect postulates that when used in combination, these cannabinoids are able to work synergistically to enhance these effects. In his paper detailing the entourage effect, Dr. E.B. Russo states, “Considered ensemble, the preceding body of information supports the concept that selective breeding of cannabis chemotypes rich in ameliorative phytocannabinoid and terpenoid content offer complementary pharmacological activities that may strengthen and broaden... applications.”

In another article published by Russo, he quotes research that hinted that full-spectrum cannabis extracts caused effects two to four times greater than single cannabinoid products alone. In the same piece, another study found that full-spectrum cannabis produced effects 330 percent higher than with single cannabinoids. However, it isn’t just the cannabinoids that may help create the entourage effect. Terpenes like limonene, myrcene, pinene, linalool, beta-caryophyllene, and others may also lend their beneficial properties to the overall effects of a cannabis treatment. Terpenes share a common molecular precursor with phytocannabinoids and evidence shows they can also interact with the body’s endocannabinoid system. Terpenes are highly bioavailable, some up to 70 percent, making them readily usable by the human body.

Over 200 have been reported so far in the cannabis plant, and many potentially display unique therapeutic benefits that may contribute meaningfully to the entourage effect. Beyond these effects, they may also provide physiological responses. Limonene can increase activity and alertness, while myrcene and linalool promoted sedation and sleep. Pinene has been shown to aid memory. Many terpenes and cannabinoids act as either antagonists or agonists of endocannabinoid receptors and seem to work together in a range of synergistic ways on this system of neurotransmitters. Ultimately, it is a personal choice whether you are best using a product created with CBD isolate, like the Pure CBD line of products, or a full-spectrum product like our flagship Premium Hemp Oil, and its liquid and capsules. While those looking to avoid even trace levels of THC might choose THC free Pure CBD products, HempVAP, and Kannaway Energy Chews, other Kannaway customers can take advantage of the entourage effect by using Premium Hemp Oil and Rev!ve products.

Kannaway continues to explore new consumer products that take advantage of the beneficial effects of CBD on the body’s systems and launch them for distribution by our team of Brand Ambassadors. Learn more about Kannaway and our products here.

**READ ABOUT THE OPPORTUNITY**
Cannabinoid receptors: where they are and what they do.

Mackie K

Abstract

The endocannabinoid system consists of the endogenous cannabinoids (endocannabinoids), cannabinoid receptors and the enzymes that synthesise and degrade endocannabinoids. Many of the effects of cannabinoids and endocannabinoids are mediated by two G protein-coupled receptors (GPCRs), CB(1) and CB(2), although additional receptors may be involved. CB(1) receptors are present in very high levels in several brain regions and in lower amounts in a more widespread fashion. These receptors mediate many of the psychoactive effects of cannabinoids. CB(2) receptors have a more restricted distribution, being found in a number of immune cells and in a few neurones. Both CB(1) and CB(2) couple primarily to inhibitory G proteins and are subject to the same pharmacological influences as other GPCRs. Thus, partial agonism, functional selectivity and inverse agonism all play important roles in determining the cellular response to specific cannabinoid receptor ligands.

CBD – three little letters that just might revolutionize how people view medication and their options for treatment.

A survey from April of this year showed that 55% of Americans regularly take prescription medication. That percentage might not seem overly alarming because prescription medication has become so normalized. However, the negative ramifications of prescription medications, including the exploding opioid crisis, underscore the sometimes-lethal consequences of our fixation on prescription drugs. Unfortunately, many alternative options for treatment, i.e. homeopathic remedies, do not generally have the research or scientific support to be seen as a viable and effective alternative.

Enter CBD.

Over the course of this year (and many years prior) Cannabidiol has been shown to be a potential therapy for:

- Anxiety
- Epilepsy/Seizure
- Psychotic Disorders
- Stroke Rehabilitation
- PTSD
- Pain
- Colitis
• High Blood Pressure
• Liver Injury

Also, study after study has demonstrated CBD does not get you high. As such, this powerful therapy should not be associated with rolling a joint to mellow out; it has real potential to be a legitimate treatment.

This is great news given that the conditions listed above are generally treated by prescription medication, which can cause severe side effects and opioid addiction.

**CBD studies with the greatest impact over the past year**

Over the past year, hundreds of CBD-related studies were conducted across dozens of countries and institutions. Many of them contribute to the growing understanding — and acceptance — of CBD.

We decided to call out 17 of the studies that stood out among the most important CBD studies of the year. While this is not a comprehensive list, it does highlight some of the critical studies conducted by important researchers in this field.

The studies discussed below continue to pave the way for alternative ways to medicate with CBD and voice urgent need for more research into CBD.

If you’d like to see a graphical representation of the information found in this report, we encourage you to take a look at our visualization of CBD studies.

Table of Contents

- CBD Research Round-Up
- CBD and Treatment-Resistant Seizures
- Seizures in Children and How CBD Therapy Might Help
- Can CBD Help Manage Fear?
- Afraid of Public-Speaking? CBD Might Help
- Potential Anti-Panic Actions of CBD
- Does CBD Reduce High Blood Pressure?
- Does CBD Get You High?
- CBD Doesn’t Make You Burn Through a Box of Oreos
- CBD’s Potential Lack of Effect on Anxiety
- CBD’s Relevance to Schizophrenia
- Cannabis vs. Opioid-Based Pain Medication: Patient Self-Report
- CBD and Opioid Use: First Long-Term Study
- CBD and Irritable Bowel Disease
- Liver Injury and CBD’s Potential Healing Effect
- A Potential Aid in Brain Recovery After a Stroke
- Pain and CBD’s Potential Effect
- What’s Next?

**CBD Research Round-Up**

Authors: Kerstin Iffland and Franjo Grotenhermen; nova-Institut, Hürth, Germany
A logical start to this list is an overall update on CBD. Published in June, this review evaluated a massive amount of existing research, data, and studies with the intent to update and synthesize vast amounts of data.

**Overarching Conclusions**

- CBD is safe to use
- There is a major need for more research as the majority of studies were performed for treatment of epilepsy and psychotic disorders
- Most common side effects reported are tiredness, diarrhea, and changes of appetite/weight.
- CBD has comparatively fewer side-effects compared with prescription medication
- The fewer side-effects could help increase patient-adherence to treatment
- CBD can be used as a supplemental therapy

To put the CBD side-effects in perspective, other drugs used for the same medical condition have far more negative side-effect profiles. This is particularly important as choosing a treatment with fewer side-effects could help ensure patients actually follow their treatment plans.

As to the safety of CBD use, the authors stated that the “safety profile is already established in a plethora of ways” and the breadth of their review serves to substantiate and build upon this notion.

**CBD and Treatment-Resistant Seizures**

Authors: G. Pesáñez-Ríos, L. Armijos-Acurio, R. Jimbo-Sotomayor, S.I. Pascual-Pascual, G. Pesáñez-Cuesta
An Explanation of Epilepsy

Having a medical condition is difficult enough, but if that condition doesn’t respond to medical treatment, life can become a constant battle. **Refractory epilepsy** is also known as uncontrolled or drug-resistant epilepsy. This means that a person who is suffering from refractory epilepsies is not responding to traditional medicine and thus is unable to effectively manage his or her neurological disorder.

As of 2014, **50 million people worldwide suffer from epilepsy** (more than Parkinson’s disease and cerebral palsy combined), and it is the **fourth most common neurological disorder** in the United States. Of that 50 million, approximately 1/3 – over 16 million – are unresponsive to antiepileptic medication and other medical treatments.

Published on August 16, 2017, the study **Cannabidiol: its use in refractory epilepsies** explores the **use of CBD as a therapy** on patients whose seizures had been non-responsive to prior treatments.

**Study Parameters and Results**

A group of 15 patients who received CBD over a period ranging from one month to one year were surveyed to gather various data. The researchers sought information about the patient and the caregiver, changes observed in the seizures, neuropsychological effects, side effects and the family’s overall perception following the use of cannabidiol. This simple observational study identified some very encouraging findings:

- Frequency of seizures: **Decreased in 40% of patients**, disappeared completely in 27% of patients.
• Level of patient-control over seizures: 60% of patients were able to control 50% of their seizures.
• Neurocognitive changes: Many patients experienced improvements in behavior, language, sleep, and eating habits. Moreover, 100% of the patients reported that their mood had improved after the use of CBD.
• Side effects: Most common were drowsiness and fatigue.

The impact of this study could be far-reaching both for patients with refractory epilepsy as well as patients with epilepsy who feel compelled to try other treatment methods.

Seizures in Children and How CBD Therapy Might Help
Authors: Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., and Stephen Wright, M.D.; Cannabidiol in Dravet Syndrome Study Group

Similar to the study above, this study explores the effects of CBD therapy in relation to seizures, but is focused on children with Dravet Syndrome. Dravet Syndrome is a rare genetic epileptic neurological disorder that develops in the first year of a child’s life. It can cause developmental disabilities and is currently treated by finding the best mix of medications to manage the child’s seizures. Unfortunately, traditional medications and treatments generally seek only to minimize the symptoms which is, unfortunately, typically a lost cause as the seizures from this condition are refractory.

Trial Parameters and Process

The parameters of this trial are particularly impressive and add to the integrity of the results:
Double-blind
Placebo-controlled
Subject pool of 120 children and young adults with Dravet syndrome and drug-resistant seizures

Over the course of a 14-week treatment period, the subjects were randomly assigned either a daily dose of CBD oral solution based on body weight or a placebo. The doses were given in conjunction with each subject’s standard antiepileptic treatment.

Results

While the rate of non-convulsive seizures did not change, the CBD-treated convulsive seizures decreased from 12.4 to 5.9 percentage points – almost half. The placebo group only decreased by 0.8. In addition, 5% of patients who were given CBD became seizure free, compared with none in the placebo group. It’s important to note that the CBD group did experience more severe side-effects, including vomiting and fever. However, these side-effects should be put in context. An astonishing 62% of the CBD group reported an significant increase in their overall condition, compared with on 34% of the placebo group.

The results are certainly compelling. However, the adverse side-effects warrant a more comprehensive, long-term study to investigate the continued use of CBD for Dravet Syndrome sufferers.

Can CBD Help Manage Fear?
Authors: Stern CAJ, da Silva TR, Raymundi AM, de Souza CP, Hiroaki-Sato VA, Kato L, Guimarães FS, Andreatini R, Takahashi RN, Bertoglio LJ; University of Parana, University of São Paulo, Federal University of Santa Catarina
Fear is something everyone can relate to. In fact, over 25 million people in the U.S. will experience PTSD at some point in their lives. This study looked at how CBD might weaken fear-response related to an adverse memory (like PTSD). The results of this study, while based on fear in a more esoteric sense, do appear to suggest that CBD may one day play a vital role in the management of such a prevalent disorder.

The furry subjects, 277 Wistar rats, were given a dose of CBD immediately after receiving a small electric shock. The CBD-treated subjects were found to spend less time frozen in fear when reintroduced to the context of the fearful event. This means the CBD disrupted consolidation (or more simply put: memory strengthening) of their specific and long-term fear memory.

CBD was also found to disrupt the consolidation of generalized fear memories when administered immediately after the acquisition of such fear memory. Interestingly, the timing of the administration of CBD was vital as the results demonstrated that delayed administration of the CBD dose did not have the same effective result that immediate administration did. The findings of this study could have a huge impact on PTSD management.

Afraid of Public-Speaking? CBD Might Help
Authors: Antonio W. Zuardi, Natália P. Rodrigues, Angélica L. Silva, Sandra A. Bernardo, Jaime E. C. Hallak, Francisco S. Guimarães, and José A. S. Crippa; University of São Paulo, National Institute of Science and Technology for Translational Medicine, National Council for Scientific and Technological Development
Fear of public speaking, also known as Glossophobia, is incredibly common and most people have experienced it at some point in their lives. This double-blind study involved a total of 60 males and females between the ages of 18 and 35. The subjects were divided into 5 groups who randomly received either a placebo, CBD in 100mg, 300mg or 900mg, or clonazepam (a medication used to treat panic disorders) following the experimental procedure in the graphic below:

Each participant gave a speech in front of the other participants, after which he or she again filled out the questionnaire on anxiety level (see graphic) and again had his or her blood pressure and heart rate taken.

Results

Clonazepam was the obvious front runner, consistently reducing anxiety in a more sedative way than the placebos and CBD administration. However, CBD at a dosage of 300mg was shown to significantly reduce subjective anxiety in the post-speech phase. The same was not true for the 100mg and 900mg dosage. This study’s true focus was the varied dosage; seeking whether administration of CBD produces an “inverted U-Shaped dose response.”

We spoke with Antonio Zuardi, who told us this phrase “refers to a concept that a given drug is effective with an intermediate dose, but not with smaller or larger doses.” CBD did indeed produce such a response.

As such, Zuardi noted that “These findings stress the importance of the careful choice of dose ranges when investigating the potential therapeutic effects of CBD.”
The dosing is obviously vital but the real-life impact of this study is that CBD could be used to manage anxiety.

Potential Anti-panic Actions of CBD
Authors: Vanessa P. Soares and Alline C. Campos

This review opens strong, stating: “Panic disorder (PD) is a disabling psychiatry[sic] condition that affects approximately 5% of the worldwide population.” The percentage itself might sound small, but it is actually 355 million people. This is a staggering number of people who suffer from anxiety.

The authors analyzed prior human and animal studies to consolidate the information and make an overarching determination as to the therapeutic effect of cannabinoids, particularly, CBD. The article looked to a multitude of findings from prior studies such as human anxiety in public speaking and electrical stimulation in animal subjects.

Long story short, this article confirmed that CBD appears to be a promising treatment for panic disorders.

The most compelling conclusion is CBD is not habit-forming and doesn’t decrease tolerance. Thus, it could be a solid alternative for “high potency benzodiazepines and antidepressant drugs in PD patients who are resistant to the current treatments.” This is incredibly encouraging not only for those with panic disorder but also those with varying types of anxiety who currently rely on psychiatric medications.

Does CBD Reduce High Blood Pressure?
Authors: Khalid A. Jadoon, Garry D. Tan, and Saoirse E. O’Sullivan
High blood pressure is a globally ubiquitous issue. This study explores the connection between CBD and a reduction in blood pressure. It is particularly unique as it is noted that “there are no dedicated studies in humans to date, to our knowledge, looking at the effect of CBD on either resting cardiovascular measurement or on the responses to stress, with continuous monitoring of CV parameters.”

In a randomized, placebo-controlled, double-blind, crossover study, nine healthy male volunteers were given either 600 mg of CBD or a placebo. They were then monitored for changes in their cardiovascular system.

Using stress tests, such as math without a calculator, cardiovascular outputs were monitored. The study found that CBD reduced resting systolic blood pressure and stroke volume. It also “blunted the blood pressure response to stress[...].”

High blood pressure has a multitude of potential treatments, including diet and exercise. This study essentially adds CBD to the list. The data from this research is also important as information for potential side-effects of CBD.

Does CBD Get You High?

Authors: Gerhard Nahler, Franjo Grotenhermen, Antonio Waldo Zuardi, and José A.S. Crippa; Department of Neuroscience and Behavior, University of São Paulo Ribeirão Preto, Brazil and Instituto Nacional de Ciência e Tecnologia Translacional em Medicina
Delta9-Tetrahydrocannabinol (“THC”) is a hurdle for CBD because THC is the primary psychoactive component in cannabis. This close association between CBD and THC is likely what causes a negative reaction to the thought of using CBD as a medical therapy. This study combats the notion that CBD causes a THC high by discussing the misinterpretations of prior studies on the subject. In fact, the researchers state that two particular prior studies “have caused much confusion and uncertainty whether oral cannabidiol (CBD) is safe and whether subjects who are treated with CBD run the risk of positive workplace tests [for THC].”

The Prior Studies

The first prior study analyzed the changes in CBD when mixed with a petri-dish simulation of stomach acids. Interpretation of the results yielded the researcher conclusion that CBD does convert to THC when exposed to stomach acids.

The second prior study also suggested CBD may convert to THC when taken orally. The conclusion was based on tests done on human volunteers.

The Misinterpretations

The study authors noted that both prior studies were severely misinterpreted. This is due to two main reasons.

1. While CBD might convert to THC under certain simulated acidic conditions, it has not been shown to actually occur in living organisms. This is a classic misinterpretation of what could happen in practicality based solely on culture-dish tests results.
2. The results of the human volunteer tests were taken out of context. Traces of THC were not only extremely minimal in the human volunteers but the alleged THC was not present in urine samples.

Author Gerhard Nahler found it most surprising that an entire group of authors were “tempted to over-interpret results.” However, he felt that misinterpretations are not entirely uncommon, stating “People overlook quite frequently that “in vitro” results may differ significantly from conditions “in vivo”, particularly in man. In vitro results are suggestions, not proofs for processes in real life.”
The current study points out that the glaring difference between CBD and THC is the inability for CBD to bind to a person’s cannabinoid brain receptors (more scientifically referred to as “CB1”). As CBD does not initiate a physiological response when combined with CB1, it “lacks cannabis-like intoxicating effects.”

**Key Takeaways**
The researchers note that while conversion to THC may occur under artificial conditions “Over 40 years of research on CBD does not suggest a conversion of CBD to delta9-THC and/or other cannabinoids in vivo after oral administration.”

To avoid misinterpretations in the future, Nahler noted “The more a result is unexpected (or presented as such as it was in the paper of Merrick et al., 2016) the more authors should be cautious when interpreting and extrapolating results.”

This is a truly impactful study for CBD use as it takes direct aim at the common-yet-faulty belief that CBD is a psychoactive compound.

**CBD Doesn’t Make You Burn Through a Box of Oreos**
**Authors:** Suzanne E.M. de Bruijn, Cees de Graaf, Renger F. Witkamp, and Gerry Jager; Wageningen University

In a test that involved giving volunteers chocolate milk to drink, this study sought the answer to a quirky question: **Does CBD (or THC) affect how humans perceive “sweet taste.”**

Spoiler: CBD does not.
Over the course of three test sessions the healthy volunteers were randomly given either a placebo, CBD, or THC and then got chocolate-wasted on several samples of chocolate milk, rating the sweetness after each.

The study found that while the THC stimulant did increase a desire to eat, the CBD did not have any effect or intervention on the subjects’ consumption.

This also helps support the prior study on this list (“CBD Does Not Get You High”) as it further debunks the notion that CBD has psychoactive effects, e.g. “the munchies.”

CBD’s Potential Lack of Effect on Anxiety
Authors: David L. Arndt and Harriet de Wit; University of Chicago
The core findings of this study is that CBD does not mute or alter the user’s mood or anxiety.

Study Parameters

Over the course of this double-blind, placebo-controlled study, 38 participants were given either a placebo or variable dose of CBD. The participants then had to complete tasks that allowed for analysis of their level of emotional “reactivity.” The tasks included:

- Perceptual sensitivity to emotional facial expressions
- Attentional bias toward emotional facial expressions
- Feelings of social rejection

This is obviously a rollercoaster of a study which found that the ups and downs of the ride did not change based on whether the participant received a placebo or CBD. The results demonstrate that CBD did not affect the subject’s anxiety.

Author Harriet de Wit found it particularly surprising that they “were unable to detect any effects of this drug, even though we went to high doses.” This indicates that CBD has, at most, a marginal effect on a user’s responses to emotional triggers.

The Impact

Again, this can be good news or bad depending on the point of view: The good: CBD might not affect how one emotionally views the world, which is great because that is one side-effect less to a potential health therapy.

The bad: CBD might not be an effective treatment for anxiety itself.
It should be noted that this study seems to be at odds with other studies in this list that say CBD is a potential therapy for anxiety. Regardless, de Wit makes the apt point: “Be skeptical about claims about various constituents of cannabis (other than THC) until we see the data from controlled studies.”

CBD’s Relevance to Schizophrenia

Authors: Osborne AL, Solowij N, Weston-Green K; Illawarra Health and Medical Research Institute, University of Wollongong

Schizophrenia is a disorder that generally requires heavy antipsychotic drugs just to manage daily life. However, this systematic review notes that such drugs “provide limited cognitive benefits,” which is extremely rough given the side effects antipsychotic drugs can have. As discussed in the review, CBD may be a possible alternative to such heavy prescription drugs.

CBD has both anti-inflammatory and anti-psychotic characteristics. Thus, the aim of the review was to evaluate literature (both preclinical and clinical) on the effects of CBD in relation to schizophrenia. The authors looked through 27 articles from the past 26 years.

The overarching theme of the literature demonstrated that CBD “improves cognition in multiple preclinical models of cognitive impairment,” which includes:

- Schizophrenia
- Alzheimer’s disease
- Fibromyalgia
- Epilepsy
- Neuro-inflammatory conditions (e.g.: Fibromyalgia)
Neurological disorders (e.g.: Epilepsy)
Due to the lack of clinical evidence, the level and effectiveness that CBD might have cannot be clearly stated. The review is nonetheless an excellent starting point for the future use of CBD in neurological treatments.

Cannabis vs. Opioid-Based Pain Medication: Patient Self-Report
Authors: Reiman Amanda, Welty Mark, and Solomon Perry; University of California, Berkeley; Kent State University; HelloMD

The goal of this study is to find an alternative to heavy pain medication, which can lead to prescription drug-abuse.

2,897 cannabis-using subjects participated in this survey. Of those who had reported using an opioid medication for pain in the six months prior to the survey, the following responses were gathered after cannabis-use:

- 97% of the sample “strongly agreed/agreed” that they are able to decrease the amount of opiates they consume when they also use cannabis
- 81% “strongly agreed/agreed” that taking cannabis by itself was more effective at treating their condition than taking cannabis with opioids

The participants also reported that cannabis was as effective in providing pain relief as other medications and did not have the “unwanted side effects.” This is incredible given that 63% of participants used cannabis to help manage pain.

While the survey is not specifically about CBD, this is an important area of research into the non-addictive nature of cannabis and lack of side effects that accompanies its use. Also, not only is it effective on its own but it can also aid the current use of opioids and decrease the need for such medication.

Ultimately, CBD may one day be a viable replacement for pain-management medications.

CBD and Opioid Use: First Long Term Study
Authors: TBD; Albert Einstein College of Medicine and Montefiore Health System
Full disclosure, this is not a published study yet, but the announcement itself is worth including in this list. A 5-year $3.8 million grant was awarded to conduct an 18-month study that will seek to answer whether medical marijuana reduces opioid use among adults with chronic pain. The study will include adults with HIV as this group, compared with the general public, has higher levels of chronic pain and opioid use. This is particularly exciting news as it is the first long-term study of this question.

CBD and Irritable Bowel Disease
Authors: Leinwand, Kristina L. DO; Gerich, Mark E. MD; Hoffenberg, Edward J. MD; Collins, Colm B. PhD; National Institutes of Health T32 Institutional Training Grant in Pediatric Gastroenterology; National Institute of Diabetes and Digestive and Kidney Diseases at the National Institutes of Health; Colorado Department of Public Health and Environment
Once diagnosed with **Inflammatory Bowel Disease (IBD)**, a person begins a lifelong battle as there is currently no cure. As noted in [this review](#), while modern medicine does tend to allow people to live relatively normal lives, the medicines used to treat IBD can have limited benefits and lose effectiveness. The review evaluated how targeting the Endocannabinoid System (ECS) could impact colitis. The ECS is a biological system within mammals that is made up of **three components**: cannabinoid receptors (the things that receive chemical signals outside the cell), endocannabinoids (small molecules that activate cannabinoid receptors), and metabolic enzymes that break down endocannabinoids after they are used. Results indicated the two main cannabinoid receptors (CB1 and CB2), along with endocannabinoids and atypical cannabinoids are “upregulated in inflammation, and their presence and stimulation attenuate murine colitis.” Put simply: manipulating the ECS can provide substantial relief from colitis.

The review notes that incidents of IBD are on the rise, which reinforces the need for research into new potential therapies. Additionally, IBD results in “an estimated annual disease-attributable direct cost in the United States in excess of $6.3 billion.” That’s 6.3 billion reasons to continue exploring novel therapies.

**Liver Injury and CBD’s Potential Healing Effect**

Authors: Yuping Wang, Partha Mukhopadhyay, Zongxian Cao, Hua Wang, Dechun Feng, György Haskó, Raphael Mechoulam, Bin Gao, and Pal Pacher; National Institute on Alcohol
This study investigated how CBD could affect subjects with liver injuries resulting from chronic and binge alcohol consumption. CBD was given to subjects (in this case, mice and human blood samples) that had been fed alcohol. In short, the analysis demonstrated that CBD lessened the elevated liver enzymes and the increased liver triglyceride. It also reduced fat droplet accumulation. Also of note, CBD improved the alcohol-induced liver metabolic impairment and abnormal retention of lipids. Essentially, CBD may be a potential therapeutic treatment for alcoholic liver diseases “associated with inflammation, oxidative stress and steatosis.”

A Potential Aid in Brain Recovery After a Stroke
Authors: Ceprián M, Jiménez-Sánchez L, Vargas C, Barata L, Hind W, Martínez-Orgado J; Universidad Complutense de Madrid; Instituto de Investigación Puerta de Hierro Majadahonda, Instituto de Investigación Puerta de Hierro Majadahonda; GW Research Ltd; Instituto de Investigación Puerta de Hierro Majadahonda
Arterial Ischemic Stroke occurs when blood flow in an artery to the brain is blocked due to narrowness of the artery or the formation of a blood clot. Neonatal (i.e. newborn) Arterial Ischemic Stroke grimly means there is a condition specific to infants. Woefully little is known about NAIS, but it can certainly lead to lifelong disabilities and/or brain injury. Currently, there is no effective treatment. This study demonstrated CBD can reduce brain damage and improve recovery, at least in the neonatal Wistar rat subjects studied. Analyzing the effects to the brain via MRI, behavioral tests, and other system studies, the researchers found that CBD administration after induced artery blockage led to “long-term functional recovery.” CBD reduced all of the following: the loss of neuronal structure and function, the abnormal increase of astrocytes (a certain type of cell in the brain), cell death and damage, and inflammation of the nervous tissue.

With more clinical studies this treatment could become a reality for human newborns.

Pain and CBD’s Potential Effect
Authors: Karina Genaro, Débora Fabris, Ana L. F. Arantes, Antônio W. Zuardi, José A. S. Crippa, and William A. Prado; University of São Paulo; National Institute of Science and Technology for Translational Medicine
The phrase “affective-motivational dimension,” refers to the relationship between pain and perception; a rather complex relationship. Pain is multidimensional; it is “an experience that has somatosensory, affective, motivational and cognitive characteristics.” Pain also affects several regions of the brain, which makes the relationship between pain and perception difficult to analyze.

This study analyzed whether the application of CBD has an effect on pain in the varied ways it can be perceived and experienced. The research yielded several results. Most notable was “systemic” application of CBD reduces mechanical allodynia in the injured subjects. The researchers concluded that there is evidence “CBD influences different dimensions of the response of rats to a surgical incision.” This is one of the first studies to show that CBD can have an effect on the perception of pain, which paves the way for future research in this area.

What’s Next?
The findings from these studies are broad, ranging from treatment of serious disorders to quirky ancillary information. Ultimately, these aren’t the first studies to be done on the efficacy of CBD as a medical therapy.

Fundamentally, the true importance of these studies and reviews is the fact that many of them, and the researchers behind them, are building from earlier findings, theories, and research efforts. Their impact is not only the actual results but the way those results echo into the CBD research field. These studies are a call to action, reflecting the vast need to dig deeper into the potential benefits of CBD as an alternative treatment for so many disorders.
More research, trials, and studies are needed to fully understand the long-term effects and benefits of this potentially game-changing way to approach treatments. This year was progressive in changing the perception of cannabidiol and highlighting its potential uses; here’s looking to 2018 to continue working toward research growth!

Short-Term Efficacy of CBD-Enriched Hemp Oil in Girls with Dysautonomic Syndrome after Human Papillomavirus Vaccination.


Show full citation

Abstract

BACKGROUND: Cannabidiol (CBD)-based treatments for several diseases, including Tourette’s syndrome, multiple sclerosis, epilepsy, movement disorders and glaucoma, are proving to be beneficial and the scientific clinical background of the drug is continuously evolving.

OBJECTIVES: To investigate the short-term effect of CBD-enriched hemp oil for relieving symptoms and improving the life quality (QOL) in young girls with adverse drug effects (ADRs) following human papillomavirus (HPV) vaccine.

METHODS: In this anecdotal, retrospective, "compassionate-use", observational, open-label study, 12 females (age 12-24 years) with severe somatoform and dysautonomic syndrome following HPV vaccination were given sublingual CBD-rich hemp oil drops, 25 mg/kg per day supplemented by 2-5 mg/ml CBD once a week until a maximum dose of 150 mg/ml CBD per day was reached over a 3 month period. Patients' quality of life was evaluated using the medical outcome short-form health survey questionnaire (SF-36).

RESULTS: Two patients dropped out due to iatrogenic adverse events and another two patients stopped the treatment early due to lack of any improvement. SF-36 showed significant benefits in the physical component score (P < 0.02), vitality (P < 0.03) and social role functioning (P < 0.02) after the treatment. The administration of hemp oil also significantly reduced body pain according to the SF-36 assessment. No significant differences from the start of treatment to several months post-treatment were detected in role limitations due to emotional reactions (P = 0.02).

CONCLUSIONS: This study demonstrated the safety and tolerability of CBD-rich hemp oil and the primary efficacy endpoint. Randomized controlled trials are warranted to characterize the safety profile and efficacy of this compound.
Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System

Shenglong Zou and Ujendra Kumar

Abstract

1. Introduction

The plant Cannabis sativa, better known as marijuana, has long been used for medical purpose throughout human history. The first record can be traced back to ancient China around 5000 years ago, where extracts of the plant were used for relief of cramps and pain [1]. The widely-documented uses of marijuana include anti-nociception, anti-inflammation, anticonvulsant, anti-emetic, as well as recreational use, which has largely limited its medical application [1,2]. Not until half a century ago, the first light was shed on the myth of the versatility of marijuana by the discovery of Δ⁹-tetrahydrocannabinol (THC), the main psychoactive component of approximately 70 phytocannabinoids identified in the plant [3,4]. This milestone discovery led to the generation of a variety of synthetic cannabinoids with similar or distinct structures to phytocannabinoids, which finally led to the identification and successful cloning of the cannabinoid receptor 1 (CB1R) [5,6,7]. Not long after that, another cannabinoid receptor (CBR) was identified and cloned, later termed as the cannabinoid receptor 2 (CB2R) [8]. Despite only CB1R and CB2R are widely-acknowledged as CBRs, several other receptors, ranging from other G protein-coupled receptors (GPCRs) to ion channel and nuclear receptors, have been reported to interact with cannabinoids [9,10]. Meanwhile, N-arachidonoyl-ethanolamine (AEA; anandamide) and 2-arachidonoylglycerol (2-AG) have been discovered to serve as endogenous agonists of CBRs, namely endocannabinoids [11,12,13]. These two compounds are the first to be identified and remain the best-studied endocannabinoids, which are both derivatives of arachidonic acid [3]. In recent years, much attention has been drawn to utilizing marijuana extracts in medicine [14].
Due to the clinical application of marijuana and the non-psychoactive nature of most phytocannabinoids except THC, the therapeutic potential of these compounds has been greatly appreciated [14]. Although this area of research is quite controversial and debatable, several phytocannabinoids, especially cannabidiol (CBD), have been suggested to exert beneficial effects in various pathological conditions, including inflammation, cancer, addiction and epilepsy [14,15,16,17].

2. Cannabinoid Receptors

Due to the lipophilic nature of cannabinoids, it was initially thought that these compounds exert various biological effects by disrupting the cell membrane nonspecifically. However, following the discovery of THC and subsequent emerging of several chemically synthesized cannabinoids, the successful mapping and the pharmacological characterization of cannabinoid binding sites in the brain revealed the existence of a putative CBR and its similarity to GPCR nature, which was matched with the properties of an orphan GPCR that is now known as CB1R [4,5,6,7,18].

CB1R is encoded by the gene CNR1 and consists of 472 amino acids in humans (473 amino acids in rat and mouse, with 97–99% amino acid sequence identity among these species). Several variations of CNR1 have been associated with Cannabis dependence [19,20,21]. Two recent studies have described the crystal structure of the antagonist-bound CB1R independently [22,23]. A study published earlier this year described the structural changes of CB1R upon agonist binding, unraveling the conformational mechanism of the well-known diverse structures and signaling bias of CB1R agonists [24]. In addition to the canonical long form of the CB1R, two additional isoforms with shorter N-terminus have been reported, both resulting from alternative splicing [25,26]. Recently, the different expression patterns of these three isoforms have been characterized at the mRNA level in human brain, skeletal muscle, liver, and pancreatic islet [27]. The full-length CB1R dominates in the brain and skeletal muscle, whereas the CB1Rb (with 33 amino acid deletion at the N-terminus) shows a higher expression level in the liver and pancreatic islet cells where it is involved in metabolism [27]. The pharmacological and physiological properties of the two splice variants have yet to be explored, as current studies accomplished in non-human models revealed discrepancies [25,28,29].

CB2R is encoded by the gene CNR2, which consists of 360 amino acid in humans. It shares only 44% sequence homology with CB1R at the protein level. The CB2R also has greater species differences among humans and rodents in comparison to CB1R, as the amino acid sequence homology is slightly above 80% between humans and rodents [30,31]. In humans, two isoforms of the CB2R have been identified, with one predominantly expressed in testis and at lower levels in brain reward regions, whereas the other is mainly expressed in the spleen and at lower levels in the brain [31]. The testis isoform has a promoter that is 45 kb upstream from the spleen isoform [31]. Thus far, four rat CB2R isoforms and two mouse isoforms have been discovered [30,31].
3. Endocannabinoid System

The successful identification and cloning of the CB1R prompted the discovery of its first endogenous agonist, AEA, in 1992 [13]. The fact that AEA cannot fully reproduce the effects induced by THC leads to the discovery of another important endocannabinoid, 2-AG [11,12]. Most studies on the endocannabinoid system focus on these two endocannabinoids, despite the existence of the recently identified CB1R-interacting peptides and a series of arachidonic acid derivatives that generate endocannabinoid-like effects [32]. These two well-documented endocannabinoids, as pharmacologically characterized, possess distinct properties. AEA turns out to be a high-affinity, partial agonist of CB1R, and almost inactive at CB2R; whereas 2-AG acts as a full agonist at both CBRs with moderate-to-low affinity [7,32]. Interestingly, both AEA and 2-AG have been reported to interact with various receptors. Among those, the transient receptor potential cation channel subfamily V member 1 (TRPV1), which is activated by AEA, is the best-documented for its significant role in synaptic transmission and pain regulation, whereas the interaction of 2-AG and non-CBRs has emerged only recently [32]. Although AEA and 2-AG have significant differences in receptor selectivity, both endocannabinoids are produced on demand (although controversy exists in the case of 2-AG), in response to increased intracellular Ca\(^{2+}\) concentration [9,33,34]. However, AEA and 2-AG are synthesized, transported and inactivated in respective target tissues differently. In brief, AEA is catalyzed from N-acylphosphatidylethanolamine (NAPE) by NAPE-specific phospholipase D (NAPE-PLD) or via other routes not involving NAPE-PLD [3]. On the other hand, 2-AG is produced from diacylglycerol (DAG) by either DAG lipase (DAGL) \(\alpha\) or \(\beta\), although most if not all 2-AG mediating synaptic transmission in adult brain is generated by DAGL\(\alpha\) [35]. The rate-limiting and \(\text{Ca}^{2+}\)-sensitive step in AEA and 2-AG production, however, is the formation of NAPE and DAG, which are converted from phosphatidylethanolamine by N-acyltransferase and phosphoinositides by phospholipase C, respectively [3,35]. After release into the intracellular space, due to their uncharged hydrophobic nature, endocannabinoids are unable to diffuse freely like other neurotransmitters. Several models have been proposed to elucidate the transport of AEA: simple diffusion driven by concentration gradients generated from enzymatic degradation, endocytosis involving caveolae/lipid rafts, through certain carrier proteins like fatty acid binding proteins and heat shock protein 70 [9]. 2-AG may share the same transport system as AEA, but it is not well understood yet [36]. Once endocannabinoids are taken up by the cells, they can be degraded through hydrolysis and/or oxidation [9]. AEA is degraded by fatty acid amide hydrolase (FAAH) into free arachidonic acid and ethanolamine, whereas 2-AG is mostly hydrolyzed by monoacylglycerol lipase (MAGL) into arachidonic acid and glycerol; several other enzymes could be involved as well [9,35,37]. Oxidation of both AEA and 2-AG could involve cyclooxygenase-2 and several lipoxygenases [38].

Go to:

4. Endocannabinoid-Mediated Signaling

The basal level of 2-AG is approximately 1000 times higher than AEA in the brain. Through pharmacological manipulations, altered metabolism of 2-AG, but not AEA, exerts
remarkable effects in endocannabinoid-mediated retrograde signaling (Figure 1). Given these facts, it is proposed that 2-AG is the primary endogenous ligand for CBRs in the central nervous system (CNS) [32,34,35]. However, AEA has been shown to activate TRPV1, inhibit L-type Ca\(^{2+}\) channels independently, as well as negatively regulate 2-AG biosynthesis and physiological effects in striatum, underscoring its essential role in the regulation of synaptic transmission [39].

**Figure 1**

Simplified scheme representing endocannabinoid retrograde signaling mediated synaptic transmission. Endocannabinoids are produced from postsynaptic terminals upon neuronal activation. As the two major endocannabinoids shown in the scheme, 2-arachidonolglycerol (2-AG) is...
biosynthesized from diacylglycerol (DAG) by diacylglycerol lipase-α (DAGLα), and anandamide (AEA) is synthesized from N-acyl-phosphatidylethanolamine (NAPE) by NAPE-specific phospholipase D (NAPE-PLD). As lipids, endocannabinoids, mainly 2-AG, readily cross the membrane and travel in a retrograde fashion to activate CB1Rs located in the presynaptic terminals. Activated CB1Rs will then inhibit neurotransmitter (NT) release through the suppression of calcium influx. 2-AG is also able to activate CB1Rs located in astrocytes, leading to the release of glutamate. Extra 2-AG in the synaptic cleft is taken up into the presynaptic terminals, via a yet unclear mechanism, and degraded to arachidonic acid (AA) and glycerol by monoacylglycerol lipase (MAGL). On the other hand, AEA, synthesized in postsynaptic terminal, activates intracellular CB1R and other non-CBR targets, such as the transient receptor potential cation channel subfamily V member 1 (TRPV1). Although endocannabinoid retrograde signaling is mainly mediated by 2-AG, AEA can activate presynaptic CB1Rs as well. Fatty acid amide hydrolase (FAAH) is primarily found in postsynaptic terminal and is responsible for degrading AEA to AA and ethanolamine (EtNH₂). Although NAPE-PLD is expressed in presynaptic terminals in several brain regions, it is not clear yet whether AEA is responsible for anterograde signaling in the endocannabinoid system. Note that alternative routes exist for the metabolism of endocannabinoids, depending on the brain region and physiological conditions. Thin arrows indicate enzymatic process; thick arrows indicate translocation; blunted arrow indicates inhibition.

The first conclusive evidence supporting retrograde endocannabinoid signaling came from the observation of depolarization-induced suppression of inhibition (DSI)/excitation (DSE) [9,33,40]. Later, it was discovered that the endocannabinoid system is involved not only in short-term depression, but also in long-term depression (LTD) at both excitatory and inhibitory synapses [9,33]. Since then, the endocannabinoid system has become the most-studied retrograde signaling system in the brain.

In most cases, endocannabinoid-mediated retrograde signaling starts with the production of 2-AG, in response to increased intracellular Ca²⁺ concentration and/or activated Gq/11-coupled receptors [9,33,40]. 2-AG is then released into and traverses the extracellular space, via a mechanism not yet fully elucidated, and arrives at the presynaptic terminal where it binds to the CB1R. Activated CB1R suppresses the release of neurotransmitter in two ways: first, by inhibiting voltage-gated Ca²⁺ channels, which reduce presynaptic Ca²⁺ influx; second, by inhibiting adenylyl cyclase (AC) and the subsequent cAMP/PKA pathway, which is involved in LTD [9,33,40]. The termination of signaling requires the degradation of 2-AG by MAGL, which is expressed in selective synaptic terminals and glial cells [9,33,35].

AEA has been shown to contribute to endocannabinoid-mediated synaptic transmission in several ways. AEA is a full agonist of TRPV1, which is purported to participate in endocannabinoid signaling [32]. AEA-mediated LTD (likely via a TRPV1-dependent mechanism) has been reported in several studies [41,42,43,44,45]. The differential recruitment of 2-AG and AEA by various types of presynaptic activity has been described in the extended amygdala [42]. AEA negatively regulates 2-AG metabolism, the effect of which can be mimicked by the activation of TRPV1 [39]. There is also evidence supporting a tonic role of AEA as an endocannabinoid, since chronic blockade of FAAH leads to constant agonism of the endocannabinoid system without reducing CB1R expression, which is opposite to antagonism of MAGL [46].
Endocannabinoids are prominently involved in the suppression of synaptic transmission through multiple mechanisms, independent of synaptic nature or transmission duration [9,33]. CB1R-dependent self-inhibition in postsynaptic neurons has been observed in a subpopulation of neocortical interneurons and pyramidal neurons, as well as in hippocampal CA1 neurons [47,48,49,50]. Accumulated evidence supports endocannabinoid-mediated communication between neurons and microglia [51,52,53]. Previous studies have shown that microglial cells and astrocytes are able to produce their own 2-AG or AEA, although it is not clear yet whether these endocannabinoids are involved in the modulation of synaptic transmission [54].

In contrast, although studies have shown the presence of CB2R in the brain, the role of CB2R in endocannabinoid-mediated synaptic transmission is still largely elusive [55,56,57]. A recent study has reported that in medial prefrontal cortical pyramidal neurons, intracellular CB2R reduces neuronal firing through the opening of Ca\(^{2+}\)-activated chloride channels, suggesting its involvement in the regulation of neuronal activity [58].

5. Distribution of Cannabinoid Receptors

CB1R was first discovered in the brain. Later, by using autoradiography, in situ hybridization, and immunohistochemistry, CB1R was proven to be the most widely-expressed receptor protein from the GPCR family in the brain [9,59]. The brain regions with highest levels of CB1R expression include olfactory bulb, hippocampus, basal ganglia, and cerebellum [59]. Moderate CB1R expression is found in the cerebral cortex, septum, amygdala, hypothalamus, and parts of the brainstem and the dorsal horn of spinal cord [59]. Whereas regions like the thalamus and the ventral horn of spinal cord have low CB1R expression [59]. Several previous studies have suggested a highly concentrated expression of CB1R on presynaptic terminals, where it mediates retrograde signaling of endocannabinoids [60,61]. However, this does not preclude the existence of CB1Rs at postsynaptic sites, as functional studies demonstrate self-inhibition in neocortical neurons by endocannabinoids [33,47,49,62]. In addition to neurons, the CB1R is expressed, although to a much lower extent, in astrocytes, oligodendrocytes and microglia, where it has been shown to mediate synaptic transmission [33,54].

The CB1R is also abundantly expressed in the peripheral nervous system (PNS) as well as in the peripheral tissues in a region-specific manner [59,63,64,65] (Figure 2). In PNS, the CB1R is mostly expressed in sympathetic nerve terminals [64]. Also, the CB1R is observed in trigeminal ganglion, dorsal root ganglion, and dermic nerve endings of primary sensory neurons, where it regulates nociception from afferent nerve fibers [65,66,67]. In the gastrointestinal (GI) tract, the CB1R is enriched in both the enteric nervous system and in non-neuronal cells in the intestinal mucosa, including enteroendocrine cells, immune cells, and enterocytes [68]. Through neuronal and non-neuronal routes, the CB1R modulates the mobility of GI tract, the secretion of gastric acids, fluids, neurotransmitter and hormones, as well as the permeability of the intestinal epithelium [68]. Therefore, CB1R could control appetite from the hypothalamus in the CNS and regulate the energy balance and food intake.
from the GI tract as well. Intriguingly, hepatic CB1R also participates in the regulation of energy balance and metabolism, but in an unusual way. Normally, the expression of CB1R in the liver is very low [69]. However, under pathological conditions, the expression of CB1R in several types of hepatic cells is remarkably increased, where the CB1R actively contributes to hepatic insulin resistance, fibrosis, and lipogenesis [63]. Similarly, the CB1R is upregulated in the cardiovascular system under pathological conditions, which in turn, promotes disease progression and cardiac dysfunction [70]. Oxidative stress, inflammation and fibrosis have been observed as a result of CB1R activation in cardiomyocytes, vascular endothelial cells, and smooth muscle cells [70]. In addition to the aforementioned tissues, the expression of the CB1R has also been reported in adipose tissue, skeletal muscle, bone, skin, eye, reproductive system, and several types of cancer cells [63].

Figure 2
Major localization sites and associated functions of the CB1R in the human body. The majority of CB1Rs expressed in human body is found in the brain, where it is involved in various neurological activities. CB1Rs on the peripheral sites, although to a lesser extent, participates in the regulation of local tissue functions.
Like many other GPCRs, the CB1R is primarily localized in the cell membrane. However, besides the well-known plasma membrane localized CB1R, which is the typical distributional pattern of GPCRs, considerable observations have reported predominant intracellular localization of CB1Rs in diverse types of cells, including transfected non-neuronal cells, undifferentiated neuronal cells, and cultured hippocampal neurons [71]. Follow-up studies discovered that CB1Rs localized in intracellular compartments presumably consist of several distinct subpopulations (Figure 3). One proportion of intracellular CB1Rs comes from the continuous internalization of plasma membrane-localized CB1R [72]. Aside from the constitutive and agonist-induced internalized CB1R, accumulated evidence suggests a distinct pool of intracellularly localized CB1R, with differential functionalities from their plasma membrane-localized counterparts. These intracellular CB1Rs are in acid-filled endo/lysosomes, and do not contribute to the subpopulation expressed at the cell surface [73,74]. Moreover, the endo/lysosome-located CB1Rs increase the release of calcium from the endoplasmic reticulum and lysosomes upon activation by intracellular agonist administration [75]. Another subpopulation of CB1Rs, as suggested by several lines of evidence, is expressed in mitochondria. Previous studies have reported the effect of THC on mitochondria-associated enzymatic activity, which was attributed to the non-specific membrane disruption of lipophilic cannabinoids at that time [76]. However, recent studies have challenged this concept by demonstrating the presence of mitochondrial CB1R and its direct involvement in cellular respiration and DSI in hippocampal neurons [77]. Although there are discrepancies in the amplitude of the CB1R agonist-induced decreases in mitochondrial respiration, the existence and functionality of mitochondrial CB1Rs are undeniable [78,79,80]. Moreover, the role of mitochondrial CB1R was further expanded by several recent observations suggesting its association with cannabinoid-induced feeding behavior in hypothalamic proopiomelanocortin (POMC) neurons, memory impairment in hippocampus, and neuroprotection after cerebral ischemia/reperfusion injury [81,82,83]. These lines of evidence highlight the direct association between mitochondrial CB1R and proper functioning of mitochondria, which has been suggested to participate in many pathological conditions [84,85]. Therefore, the role of mitochondrial CB1R may not be limited to the previously discovered roles and is worth further exploration. [75,77,86].
Subcellular localization of the CB1R. Typically, the CB1R is located at cell surface and inhibits cyclic adenosine monophosphate (cAMP) formation and calcium influx upon activation. Constitutive and ligand-induced internalized CB1Rs mediate signaling pathways through β-arrestin. Intracellular-localized CB1Rs do not translocate to plasma membrane. Instead, they form a subpopulation with pharmacological properties distinct from their plasma membrane-localized counterparts. CB1Rs located on lysosomes can increase intracellular calcium concentrations through the release of internal calcium stores, and increase the permeability of lysosomes. Mitochondrial CB1Rs inhibit mitochondrial cellular respiration and cAMP production, hence regulating cellular energy metabolism.

Three years after the discovery of the CB1R, another CBR, the CB2R, was identified in macrophages in the spleen [8]. Follow-up studies revealed a predominant expression of the CB2R in immune cells and a moderate expression in other peripheral tissues, including the cardiovascular system, GI tract, liver, adipose tissue, bone, and reproductive system [10]. In contrast, the presence of the CB2R was not observed in the CNS, thus it was referred to as “the peripheral CBR” [10]. However, this concept has been challenged recently by several studies demonstrating the expression of the CB2R in the brain, albeit to a much lower extent in comparison to the immune system or the CB1R [57]. Although the expression of the CB2R in the CNS and PNS is comparatively limited, it is undeniable that the CB2R plays an active role in neurological activities, such as nociception, drug addiction and neuroinflammation [55,56]. Moreover, recent studies discovered the intracellular presence of CB2R in prefrontal cortical pyramidal neurons where it modulates neuronal excitability through the regulation of Ca²⁺-activated Cl⁻ channel [58]. In transfected human bone osteosarcoma epithelial cells, intracellularly located CB2R regulates Ca²⁺ in a faster and more potent way in comparison to CB2R expressed at cell surface [87].

Go to:

6. Cannabinoid Receptor Signaling
Both the CB1R and CB2R are members of the GPCR family and are coupled to pertussis toxin (PTX)-sensitive G\textsubscript{i/o} protein, suppress AC and the formation of cAMP upon receptor activation [10]. However, the CB1R but not the CB2R has been reported to activate other G proteins in certain circumstances in a cell type- and ligand-dependent manner [88]. The CB1R is able to stimulate specific AC isoforms via G\textsubscript{bγ} subunits [89]. Also, the CB1R stimulates cAMP via coupling to G\textsubscript{s} when the dopamine receptor 2 (D2R) is activated simultaneously in cultured striatal neurons, and when G\textsubscript{i} is blocked by PTX in transfected CHO-K1 cells, and in response to a relatively high concentration of WIN 55, 212-2 (WIN) in rat globus pallidus slices [90,91,92]. However, the same concentration of WIN but not other CB1R agonists, increases intracellular Ca\textsuperscript{2+} concentration via G\textsubscript{q/11} protein in transfected HEK-293 cells and cultured hippocampal neurons with endogenous receptor expression [93]. Moreover, in mice hippocampal slices, CB1R expressed in astrocytes is coupled to G\textsubscript{q/11}, increases intracellular Ca\textsuperscript{2+} concentrations and triggers astrocytic release of glutamate that stimulates N-methyl-D-aspartate receptor (NMDAR) on pyramidal neurons, indirectly involved in synaptic transmission [53].

Moreover, the CB1R modulates the activity of several types of ion channels [88,94]. CB1Rs have been reported to inhibit N-type Ca\textsuperscript{2+} channel in neuroblastoma cell lines, in cultured rat primary hippocampal neurons, and in mice cerebellar slices [95,96,97,98]. It has long been suggested, but proven only recently, that the CB1R regulates Ca\textsuperscript{2+} influx to inhibit γ-aminobutyric acid (GABA) release in mouse hippocampal slices via modulation of the activity of presynaptic N-type Ca\textsuperscript{2+} channel [99]. Other types of Ca\textsuperscript{2+} channels, including P/Q-type, and R-type Ca\textsuperscript{2+} channels, have been shown to be negatively regulated by CB1R in various systems [95,96,100,101]. On the other hand, the CB1R regulates the activity of G-protein-coupled inwardly rectifying K\textsuperscript{+} channels (GIRKs) as well [101,102,103]. The CB1R activates GIRK in transfected AtT-20 cells, mouse nucleus accumbens slices, and rat sympathetic neurons injected with CB1R complementary deoxyribonucleic acid (cDNA) [101,102,103].

Previous studies have shown that in a system expressing the receptor endogenously or heterogeneously, stimulation of CB1R leads to the activation of mitogen-activated protein kinase (MAPK) signaling pathways, including extracellular signal-regulated kinase 1/2 (ERK1/2), c-Jun N-terminal kinase (JNK), and p38, that are involved in the regulation of cell proliferation, cell cycle control and cell death [88,94,104]. Generally, CB1R regulates MAPK signaling in a cell type- and ligand-specific fashion [88,94,104]. For instance, CB1R-induced ERK1/2 activation can be mediated by G protein, β-arrestin, or phosphatidylinositol-3-kinases (PI3K), heavily dependent on the microenvironment and stimulus type [105,106,107]. Similarly, activation of p38 has been observed upon stimulation of CB1R in human vascular endothelial cells, transfected CHO-K1 cells, and rat/mouse hippocampal slices [108,109,110]. JNK activation has been shown in transfected CHO-K1 cells, where G proteins, PI3K and Ras were involved in the transduction [109]. Moreover, JNK activation was also observed in Neuro2A cells with endogenous expression of CB1R, and may be related to CB1R-mediated neurite outgrowth [111].

In addition to the typical G protein-dependent signaling seen with all GPCRs, the CB1R is able to signal in a G protein-independent manner through association with other molecules.
such as β-arrestin [104]. β-arrestin is a key mediator of GPCR desensitization. Following receptor phosphorylation by GRK, β-arrestin binds to the receptor and initiates the internalization process, during which β-arrestin could mediate signaling pathways [112]. Desensitization of the CB1R has been shown to be β-arrestin 2-dependent in various systems [113,114]. It has been reported in transfected HEK-293 cells that β-arrestin 2-mediated desensitization but not internalization of CB1R determines the time course of ERK1/2 phosphorylation upon CB1R activation [115]. Furthermore, follow-up studies revealed a positive correlation between the extent of β-arrestin-mediated signaling and the duration of CB1R interaction with β-arrestin at the cell surface in a ligand-specific manner [106]. Studies using β-arrestin 2 knockout mice have suggested a critical role of β-arrestin 2 in the regulation of CB1R activity [116,117]. The β-arrestin 2 knockout mice displayed a comparable expression level of CB1R yet an increased sensitivity to THC, featuring enhanced antinociception and decreased tolerance [116,117]. A recent study suggested a role of β-arrestin 1 in the phosphorylation of ERK1/2, MAPK kinase 1/2 and the proto-oncogene tyrosine-protein kinase Src in response to a CB1R allosteric modulator ORG27569, underscoring a signaling mechanism that is largely dependent on stimulus [118].

The PI3K/Akt pathway is another key regulator of cell growth and death aside of MAPK signaling. In rat primary cultured astrocytes, human astrocyte cell line, and transfected CHO-K1 cells, the CB1R has been shown to activate the PI3K/Akt pathway, which is responsible for the CB1R-induced protective effects on cell survival [105,111,119]. In rat oligodendrocyte progenitors, the CB1R promotes cell survival against nutrient deprivation and modulate cell differentiation via the PI3K/Akt pathway [120,121]. Similarly, in rat cortical cultured neurons, a CB1R selective agonist, HU-210, exerts neuroprotective effects against the neurotoxin (S)-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid through activation of the PI3K/Akt pathway but not MAPK pathways [122]. A previous study in mice demonstrated that acute administration of THC activated the PI3K/Akt pathway, but not ERK1/2 in several brain regions [123]. A recent study in huntingtin knock-in striatal neuronal cells showed that CB1R protected neurons against excitotoxicity via PI3K/Akt signaling-mediated increase in brain-derived neurotrophic factor (BDNF) expression [124]. In addition, CB1R-mediated PI3K/Akt activation has also been shown to modulate oocyte maturation and embryonic development [125] (Figure 4).
CB1R-modulated major signaling pathways. Typically, the CB1R is coupled to $G_{i/o}$ and inhibits the activity of adenyl cyclase (AC), formation of cyclic adenosine monophosphate (cAMP), and the activity of protein kinase A (PKA). Under certain circumstances, the CB1R can switch its coupling of G protein from $G_{i/o}$ to $G_s$ or $G_q$. The CB1R is able to suppress calcium influx via voltage-gated calcium channel (VGCC). Several mitogen-activated protein kinases (MAPKs), including ERK1/2, p38, and JNK, are activated by the CB1R. The phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) pathway is activated by CB1R as well. Depending on the ligand and subcellular environment, the outcome of CB1R-mediated signaling could be promotion of cell survival or cell death. Arrows indicate stimulation; blunted arrows indicate inhibition.

7. Physiological and Pathological Roles of the CB1R

Given the widespread distribution of CB1Rs in the human body, it is reasonable for one to speculate a broad spectrum of physiological roles of the CB1R [3,9,63,126]. Indeed, the CB1R and the endocannabinoid system are largely involved in various aspects of central neural activities and disorders, including appetite, learning and memory, anxiety, depression, schizophrenia, stroke, multiple sclerosis, neurodegeneration, epilepsy, and addiction.
The CB1R is also involved in physiological and pathological conditions in the PNS and peripheral tissues, including pain, energy metabolism, cardiovascular and reproductive functions, inflammation, glaucoma, cancer, and liver and musculoskeletal disorders [63]. The expression of CB1R remarkably fluctuates in many pathological conditions, underscoring its critical role in a wide spectrum of biological activities [69]. Interestingly, in some cases, both positive and negative alterations in CB1R expression and functionality have been reported [69]. Moreover, the administration of CB1R agonists exert biphasic effects in several conditions [128]. On the other hand, the widespread presence of the CB1R limits the therapeutic application of CB1R ligands due to various side effects. These facts underscore the significance of understanding and manipulating the endocannabinoid system in a condition-specific manner.

CB1R has been found to inhibit GABA and glutamate release from presynaptic terminals, which confers the CB1R with the ability to modulate neurotransmission [60,129]. This has been proposed as a plausible underlying mechanism of CB1R-mediated neuroprotection against excitotoxicity, a prominent pathological process of many neurological disorders, including epilepsy and neurodegenerative diseases [34,130,131]. To date, numerous studies have shown that the CB1R plays a neuroprotective role against excitotoxicity induced by various stimuli [131,132,133,134]. It has been demonstrated recently that in mouse brain, the neuroprotective effect exerted by CB1R against excitotoxicity is restricted to the CB1R population located on glutamatergic terminals [130]. In addition to the prominent inhibitory effects on Ca\(^{2+}\) influx and glutamate release, CB1R-mediated neuroprotection also involves inhibition of nitric oxide (NO) production, reduction of zinc mobilization, and increase of BDNF expression [134,135,136]. Recent studies have implicated a direct physical interaction between CB1Rs and NMDARs in the presence of histidine triad nucleotide-binding protein 1, which allows CB1Rs to negatively regulate NMDAR activity and protects neural cells from excitotoxicity [136,137].

Specifically, altered expression of the CB1R and other elements of the endocannabinoid system have been observed in various neurodegenerative diseases, such as Alzheimer’s disease (AD), Parkinson’s disease (PD) and Huntington’s disease (HD) [3]. The upregulation of the CB1R and endocannabinoid system activity has been observed in the basal ganglia of experimental models of PD, which could be a mechanism to compensate the degenerated dopaminergic neurons of the substantia nigra, or a pathological process that contributes to the worsening of the disease [138]. Interestingly, decreased endocannabinoid system activity has also been reported in PD models [128]. Moreover, both the FAAH inhibitors and CB1R antagonists have been shown to alleviate the motor symptoms in PD models [128]. Similarly, although changes of CB1R expression in AD patients or animal models are still controversial, the activation of the CB1R has been shown to prevent amyloid β-induced neurotoxicity in several cell models [139,140,141,142,143,144]. In addition, the activation of the CB1R has been reported to be beneficial in AD animal models with memory deficits and cognitive disorders [145,146,147]. On the other hand, studies have emphasized the beneficial potentials of the CB1R in HD pathogenesis. In 1993, decreased expression of the CB1R was first reported in the substantia nigra of HD patients via autoradiography [148]. Further studies revealed a progressive loss of CB1Rs as an early sign of HD, which occurred before
the onset of actual neurodegeneration, and hastened the worsening of HD [149]. This observation was confirmed at the mRNA level as well as with CB1R immunoreactivity in several transgenic HD mouse models (reviewed in [3]). A recent study described downregulation of the CB1R not only in medium spiny projection neurons (MSNs) but also in a subpopulation of interneurons that are selectively preserved in both transgenic HD mice and HD patients [150]. Delayed loss of CB1Rs in HD transgenic mice R6/1 was seen in enriched environment, accompanied by delayed onset of motor disorders and disease progression [151]. Moreover, in HD transgenic mice R6/2, CB1R knockout leads to the worsening of motor performances, increased susceptibility to 3-nitropropionic acid, and exacerbated striatal atrophy and Huntingtin (Htt) aggregates [133,152]. Selective increase in CB1R expression in MSNs improves the survival of excitatory projection neurons, but does not promote the motor performances of HD transgenic R6/2 mice [153]. Administration of THC has been reported to ameliorate motor disorders, striatal atrophy, and Htt aggregates in transgenic mice, although controversy exists [133,154]. Activation of the CB1R inhibits glutamate release while increases BDNF release from presynaptic terminals in mice [131]. Further investigation in HD cell models revealed that CB1R activation can protect striatal cells against excitotoxicity through increased BDNF expression via PI3K/Akt pathway [133]. These observations support a critical and possibly beneficial role of the CB1R in neurodegenerative diseases.

The historical record of the anti-epileptic effects of the CB1R dates back centuries [1]. Case reports on the beneficial effects of cannabinoids on epileptic patients became available only after the identification of THC [155,156]. However, studies also suggested increased seizure frequency after marijuana smoking [157]. This paradoxical effect of cannabinoids on epilepsy is not only seen in human studies but has also been reported in animal models [158,159]. Activation of the CB1R by AEA has been shown to inhibit electroshock-induced seizures in rats [159]. Conversely, CB1R activation in FAAH knockout mice displays increased susceptibility to kainic acid-induced seizures [158]. The alteration of the endocannabinoid system following epilepsy is cell type-specific. This concept is supported by previous animal studies showing that CB1R retrograde signaling is selectively enhanced at inhibitory but not excitatory synapses, resulting a persistent potentiation of DSI but not DSE in febrile seizures, which leads to hyper-excitability of neurons, thus contributing to the exacerbation of seizures [160,161]. Moreover, this CB1R-mediated enhanced suppression of inhibitory neurons is phase-dependent as well. Hippocampal tissues from epileptic patients in the acute phase of epilepsy display decreased CB1R density, especially in the dentate gyrus, whereas in patients in the chronic phase of epilepsy, an upregulation of CB1R has been observed [162,163,164,165].

Despite the low expression of CB1R in hypothalamus, cannabinoids are long known for their effects to stimulate appetite, prominently in a CB1R-dependent manner [166]. Endocannabinoids levels are increased in the rat hypothalamus during fasting and return to normal levels after food consumption [167]. The stimulation of appetite and feeding behavior is observed after direct injection of endocannabinoids and is abolished by the administration of CB1R antagonists [167]. Furthermore, activation of ventral striatal CB1Rs inhibit GABAergic neurons, resulting in a hypophagic but not an orexigenic effect [168]. A recent
study has demonstrated that CB1R-induced feeding behavior is promoted by the activation of hypothalamic POMC neurons [81]. In addition to the hypothalamus, olfactory process have been proposed to be involved in the positive regulation of CB1R-mediated food intake [169]. Moreover, crosstalk between CB1Rs and the important hormones involved in appetite regulation, including ghrelin, leptin, and orexin, has been extensively reported [68,166]. CB1Rs expressed in the GI tract also are involved in metabolic process and energy balance, as discussed in the previous section. These studies suggest that CB1R-mediated regulation of appetite involves at least two aspects: through the regulation of CNS region related to appetite, and through the modulation of metabolic hormones and digestive functions on site. Rimonabant, a CB1R antagonist, displayed remarkable anti-obesity effects, yet the accompanying psychiatric side effects lead to its withdrawal from the market [170]. An up-to-date review by Koch have summarized the recent progress on elucidating the role of CB1R in appetite control [171].

The regulation of pain is one of the earliest medical applications of cannabinoids [1,2]. Numerous studies have documented the analgesic effects of cannabinoids in different types of pain, including chemical, mechanical, and heat pain, as well as neuropathic, inflammatory, and cancer pain [172,173]. The endocannabinoid system also is involved in the regulation of nociception [3]. A newly published review paper has discussed the preclinical and clinical studies on the role of endocannabinoids in the control of inflammatory and neuropathic pain in details [173]. In addition to the CB1R, there also is evidence supporting the involvement of the CB2R and TRPV1 in cannabinoid-mediated regulation of pain [174,175]. Furthermore, the phytocannabinoids have drawn much attention nowadays in the field of antinociception and other neurological disorders. CBD, for instance, has been shown to module Chronic pain in several studies [173]. The drug with brand name Sativex, containing equal amount of THC and CBD, is used to treat several kinds of multiple sclerosis associated symptoms including chronic pain [176]. Despite the fact that CBD has negligible affinity to the CB1R and CB2R, recent studies have suggested that it is an allosteric modulator and an indirect antagonist of CBRs, with the ability to potentiate the effect of THC [177].

Cannabinoids used in cancer are best-known for their palliative effects, including reducing nausea and vomiting, alleviating cancer pain, and stimulating appetite [178,179]. It has been argued that cannabinoids can exert anti-tumor effects directly through the inhibition of cell proliferation and induction of apoptosis, or indirectly through the inhibition of angiogenesis, invasion and metastasis [180]. Numerous studies using synthetic/endo-/phyto-cannabinoids and endocannabinoid system regulators in various cancer cell lines support this notion [181]. The antitumor effects of cannabinoids have also been observed in various animal tumor models [180]. In general, an enhanced endocannabinoid system is seen in tumor tissues [179,182,183]. However, the role of upregulated endocannabinoid system activity is still controversial as contrasting results have been reported supporting a proliferative as well as an anti-proliferative role of cannabinoids on cancer cells [180,181]. Interestingly, a bimodal effect of cannabinoids on cancer cell growth has also been observed, with low concentrations being proliferative and high concentrations being pro-apoptotic [184].
8. Future Directions of Cannabinoid-Based Drug Discovery

Most cannabinoid-base drugs available now in market are THC derivatives, indicated for anorexia and emesis associated with chemotherapy [185]. As a result of systematic activation of the CB1R, the accompanying side effects always include cardiovascular dysfunction, digestion failure, neurological disorders and potential for addiction [186]. The goal of cannabinoid-based drugs is to fully explore their promising therapeutic potentials without these adverse effects and the success of Sativex provides some insights. First, phytocannabinoids may block the undesired psychoactive effects of compounds targeting CB1R. Although the exact mechanism of how a 1:1 ration of CBD to THC enables Sativex to be well-tolerated by patients is not clear, the addition of CBD certainly contributes to the prevention of the associated side effects. Second, phytocannabinoids alone possess great potential as drug targets. Excluding THC, all phytocannabinoids identified so far are non-psychoactive, making them a safer choice and a great pool for drug screening. Encouraging results have been reported on their therapeutic potential in various diseases [15,17]. Third, allosteric modulator designed to modify the effect of CB1R agonists/antagonists may be beneficial in minimizing the side effects. Research has progressed significantly towards this direction in the past few years, with several synthetic or natural compounds characterized as CB1R allosteric ligands [177,187,188,189]. A detailed review on their pharmacological properties and therapeutic potentials is available [190].

Alternative way to modulate the effect of CB1R is through heteromerization with other GPCRs [104,191]. Chimerical compounds targeting GPCR heterodimers, including delta-opioid receptor/mu-opioid receptor and somatostatin receptor 5/dopamine receptor 2, have been successfully generated and used in clinical practice [192,193,194]. CB1R has been shown to heterodimerize with several GPCRs, with distinct pharmacological properties, emphasizing its significance in different pathological conditions [104,191]. Efforts have been made to utilize these findings in drug discovery focusing on specific heterodimer complex, although recent findings on the structures of CB1R and other lipid-binding receptor suggest that the currently available bivalent ligands targeting CB1R homo- or heterodimers are unlikely to bind both protomers simultaneously [195,196]. More information on CB1R structure and dimerization interface is needed for better design of bivalent and dualsteric ligands.

Besides CB1R, other elements in the endocannabinoid system have become targets of drug discovery as well. Inhibitors of enzymes that degrade endocannabinoids, such as FAAH inhibitors, work effectively as an alternative way of CB1R activation and endocannabinoid tone enhancement, although caution should be taken in the use of these drugs due to their potential off-target activities [197]. On the other hand, CB2R is also attracting more interest, especially on the peripheral sites, where studies have shown its beneficial effects in various pathological conditions [55]. Also, recent studies have discovered its presence and significance in the CNS, revealing another exciting therapeutic potential of CB2R [56].
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9. Conclusions

The initial discovery and subsequent intensive research of the endocannabinoid system in the last three decades have revealed probably the most well-known retrograde neurotransmission system. As the main mediator of psychoactive effect of THC, CB1R has gained tremendous interest over these years. Its widespread expression and versatile functions not only support its promising potential as a drug target for various diseases, but also make the undesired side effects almost inevitable. This obstacle leads researchers to pay more attention to the long-ignored CB2R and other endo-/phyto-cannabinoids. Moreover, as a neuromodulator, the crosstalk between endocannabinoid and other neurotransmitter systems, via either local neural circuits, or receptor heteromerization, or downstream signaling, has been emphasized. Fruitful studies have been generated, unraveling the complexity of the whole endocannabinoid system. It is critical to keep in mind that the study of the endocannabinoid system should be region- and condition-specific, along with the consideration of other neurotransmission systems.

Acknowledgments

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Abbreviations

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<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>THC</td>
<td>$\Delta^9$-tetrahydrocannabinol</td>
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<td>CBR</td>
<td>Cannabinoid receptor</td>
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<tr>
<td>AEA</td>
<td>$N$-arachidonoyl-ethanolamine</td>
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<td>2-AG</td>
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<tr>
<td>GPCR</td>
<td>G protein-coupled receptor</td>
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<td>TRPV1</td>
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<tr>
<td>NAPE</td>
<td>N-acyl-phosphatidylethanolamine</td>
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<td>Medium spiny projection neuron</td>
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Author Contributions

Shenglong Zou wrote the manuscript. Ujendra Kumar edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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