



# CBD

## Scientific Research Abstracts

Epilepsy Curr. 2014 Sep;14(5):250-2. doi: 10.5698/1535-7597-14.5.250.

**Cannabidiol: promise and pitfalls.**

Welty TE, Luebke A, Gidal BE

Abstract

Over the past few years, increasing public and political pressure has supported legalization of medical marijuana. One of the main thrusts in this effort has related to the treatment of refractory epilepsy-especially in children with Dravet syndrome-using cannabidiol (CBD). Despite initiatives in numerous states to at least legalize possession of CBD oil for treating epilepsy, little published evidence is available to prove or disprove the efficacy and safety of CBD in patients with epilepsy. This review highlights some of the basic science theory behind the use of CBD, summarizes published data on clinical use of CBD for epilepsy, and highlights issues related to the use of currently available CBD products. Cannabidiol is the major nonpsychoactive component of Cannabis sativa. Over the centuries, a number of medicinal preparations derived from C. sativa have been employed for a variety of disorders, including gout, rheumatism, malaria, pain, and fever. These preparations were widely employed as analgesics by Western medical practitioners in the 19(th) century (1). More recently, there is clinical evidence suggesting efficacy in HIV-associated neuropathic pain, as well as spasms associated with multiple sclerosis (1).

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J Natl Compr Canc Netw. 2016 Jul;14(7):915-22.

**Cannabinoids for Symptom Management and Cancer Therapy: The Evidence.**

Davis MP

Abstract

Cannabinoids bind not only to classical receptors (CB1 and CB2) but also to certain orphan receptors (GPR55 and GPR119), ion channels (transient receptor potential vanilloid), and peroxisome proliferator-activated receptors. Cannabinoids are known to modulate a multitude of monoamine receptors. Structurally, there are 3 groups of cannabinoids. Multiple studies, most of which are of moderate to low quality, demonstrate that tetrahydrocannabinol (THC) and oromucosal cannabinoid combinations of THC and cannabidiol (CBD) modestly reduce cancer pain. Dronabinol and nabilone are better antiemetics for chemotherapy-induced nausea and vomiting (CINV) than certain neuroleptics, but are not better than serotonin receptor antagonists in reducing delayed emesis, and cannabinoids have largely been superseded by neurokinin-1 receptor antagonists and olanzapine; both cannabinoids have been recommended for breakthrough nausea and vomiting among other antiemetics. Dronabinol is ineffective in ameliorating cancer anorexia but does improve associated cancer-related dysgeusia. Multiple cancers express cannabinoid receptors directly related to the degree of anaplasia and grade of tumor. Preclinical in vitro and in vivo studies suggest that cannabinoids may have anticancer activity. Paradoxically, cannabinoid receptor antagonists also have antitumor activity. There are few randomized smoked or vaporized cannabis trials in cancer on which to judge the benefits of these forms of cannabinoids on symptoms and the clinical course of cancer. Smoked cannabis has been found to contain Aspergillois. Immunosuppressed patients should be advised of the risks of using "medical marijuana" in this regard.

Oncotarget. 2016 Oct 18. doi: 10.18632/oncotarget.12721. [Epub ahead of print]

**Cannabinoids synergize with carfilzomib, reducing multiple myeloma cells viability and migration.**

Nabissi M, Morelli MB, Offidani M, Amantini C, Gentili S, Soriani A, Cardinali C, Leoni P, Santoni G.

Abstract

Several studies showed a potential anti-tumor role for cannabinoids, by modulating cell signaling pathways involved in cancer cell proliferation, chemo-resistance and migration. Cannabidiol (CBD) was previously noted in multiple myeloma (MM), both alone and in synergy with the proteasome inhibitor bortezomib, to induce cell death. In other type of human cancers, the combination of CBD with  $\Delta$ 9-tetrahydrocannabinol (THC) was found to act synergistically with other chemotherapeutic drugs suggesting their use in combination therapy. In the current study, we evaluated the effects of THC alone and in combination with CBD in MM cell lines. We found that CBD and THC, mainly in combination, were able to reduce cell viability by inducing autophagic-dependent necrosis. Moreover, we showed that the CBD-THC combination was able to reduce MM cells migration by down-regulating expression of the chemokine receptor CXCR4 and of the CD147 plasma membrane glycoprotein. Furthermore, since the immuno-proteasome is considered a new target in MM and also since carfilzomib (CFZ) is a new promising immuno-proteasome inhibitor that creates irreversible adducts with the  $\beta$ 5i subunit of immuno-proteasome, we evaluated the effect of CBD and THC in regulating the expression of the  $\beta$ 5i subunit and their effect in combination with CFZ. Herein, we also found that the CBD and THC combination is able to reduce expression of the  $\beta$ 5i subunit as well as to act in synergy with CFZ to increase MM cell death and inhibits cell migration. In summary, these results proved that this combination exerts strong anti-myeloma activities.

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Perm J. 2016 Oct 12;20(4). doi: 10.7812/TPP/16-005.

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

Shannon S, Opila-Lehman J.

Abstract

INTRODUCTION:

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

CASE PRESENTATION:

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

## DISCUSSION:

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

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BMC Complement Altern Med. 2016 Sep 1;16(1):335. doi: 10.1186/s12906-016-1280-0.

### **Cannabidiol rather than Cannabis sativa extracts inhibit cell growth and induce apoptosis in cervical cancer cells.**

Lukhele S, Motadi LR.

#### Abstract

##### BACKGROUND:

Cervical cancer remains a global health related issue among females of Sub-Saharan Africa, with over half a million new cases reported each year. Different therapeutic regimens have been suggested in various regions of Africa, however, over a quarter of a million women die of cervical cancer, annually. This makes it the most lethal cancer amongst black women and calls for urgent therapeutic strategies. In this study we compare the anti-proliferative effects of crude extract of Cannabis sativa and its main compound cannabidiol on different cervical cancer cell lines.

##### METHODS:

To achieve our aim, phytochemical screening, MTT assay, cell growth analysis, flow cytometry, morphology analysis, Western blot, caspase 3/7 assay, and ATP measurement assay were conducted.

##### RESULTS:

Results obtained indicate that both cannabidiol and Cannabis sativa extracts were able to halt cell proliferation in all cell lines at varying concentrations. They further revealed that apoptosis was induced by cannabidiol as shown by increased subG0/G1 and apoptosis through annexin V. Apoptosis was confirmed by overexpression of p53, caspase 3 and bax. Apoptosis induction was further confirmed by morphological changes, an increase in Caspase 3/7 and a decrease in the ATP levels.

## CONCLUSIONS:

In conclusion, these data suggest that cannabidiol rather than Cannabis sativa crude extracts prevent cell growth and induce cell death in cervical cancer cell lines.

Clin Hemorheol Microcirc. 2016 Oct 18.

### **Experimental cannabidiol treatment reduces early pancreatic inflammation in type 1 diabetes.**

Lehmann C, Fisher NB, Tugwell B, Szczesniak A, Kelly M, Zhou J.

Abstract

#### BACKGROUND:

Destruction of the insulin-producing beta cells in type 1 diabetes (T1D) is induced by invasion of immune cells causing pancreatic inflammation. Cannabidiol (CBD), a phytocannabinoid, derived from the plant, Cannabis sativa, was shown to lower the incidence of diabetes in non-obese diabetic (NOD) mice, an animal model of spontaneous T1D development.

#### OBJECTIVE:

The goal of this study was to investigate the impact of experimental CBD treatment on early pancreatic inflammation in T1D by intravital microscopy (IVM) in NOD mice.

#### METHODS:

Seven-week-old female NOD mice were prophylactically administered daily 5mg/kg CBD or control vehicle i.p. five times weekly for ten weeks. Animals underwent IVM following confirmation of T1D diagnosis by blood glucose testing. Leukocyte activation and functional capillary density (FCD) were quantified via IVM.

#### RESULTS:

CBD-treated NOD mice developed T1D later and showed significantly reduced leukocyte activation and increased FCD in the pancreatic microcirculation.

#### CONCLUSIONS:

Experimental CBD treatment reduced markers of inflammation in the microcirculation of the pancreas studied by intravital microscopy.

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Curr Pharm Des. 2016 Aug 31.

### **From cannabis to cannabidiol to treat epilepsy, where are we?**

Lippiello P, Balestrini S, Leo A, Coppola A, Citraro R, Elia M, Russo E1, De Sarro G.

Abstract

## BACKGROUND:

Several antiepileptic drugs (AEDs), about 25, are currently clinically available for the treatment of patients with epilepsy. Despite this armamentarium and the many recently introduced AEDs, no major advances have been achieved considering the number of drug resistant patients, while many benefits have been indeed obtained for other clinical outcomes (e.g. better tolerability, less interactions). Cannabinoids have long been studied for their potential therapeutical use and more recently phytocannabinoids have been considered a valuable tool for the treatment of several neurological disorders including epilepsy. Among this wide class, the most studied is cannabidiol (CBD) considering its lack of psychotropic effects and its anticonvulsant properties.

## OBJECTIVE:

Analyse the currently available literature on CBD also in light of other data on phytocannabinoids, reviewing data spanning from the mechanism of action, pharmacokinetic to clinical evidences.

## RESULTS:

Several preclinical studies have tried to understand the mechanism of action of CBD, which still remains largely not understood. CBD has shown significant anticonvulsant effects mainly in acute animal models of seizures; beneficial effects were reported also in animal models of epileptogenesis and chronic models of epilepsy, although not substantial. In contrast, data coming from some studies raise questions on the effects of other cannabinoids and above all marijuana.

## CONCLUSIONS:

There is indeed sufficient supporting data for clinical development and important antiepileptic effects and the currently ongoing clinical studies will permit the real usefulness of CBD and possibly other cannabinoids. Undoubtedly, several issues also need to be addressed in the next future (e.g. better pharmacokinetic profiling). Finally, shading light on the mechanism of action and the study of other cannabinoids might represent an advantage for future developments.

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Clin Pharmacol Ther. 2016 Aug 10. doi: 10.1002/cpt.441.

### **The Utility of Cannabidiol in the Treatment of Refractory Epilepsy.**

Reddy DS

#### Abstract

Cannabis-derived cannabinoids such as cannabidiol (CBD) have anticonvulsant properties. Recently, there has been an emerging interest in the use of CBD-enriched products for treatment of drug-resistant epilepsy. Some pilot trials of CBD have proved beneficial for refractory epilepsy, but its efficacy is yet to be confirmed by standard placebo-controlled trials. However, the mechanisms underlying the seizure protection efficacy claims of CBD remain unclear. This review briefly describes the clinical utility of CBD in the treatment of refractory epilepsy.

### **Could cannabidiol be used as an alternative to antipsychotics?**

Fakhoury M

#### **Abstract**

Schizophrenia is a mental disorder that affects close to 1% of the population. Individuals with this disorder often present signs such as hallucination, anxiety, reduced attention, and social withdrawal. Although antipsychotic drugs remain the cornerstone of schizophrenia treatment, they are associated with severe side effects. Recently, the endocannabinoid system (ECS) has emerged as a potential therapeutic target for pharmacotherapy that is involved in a wide range of disorders, including schizophrenia. Since its discovery, a lot of effort has been devoted to the study of compounds that can modulate its activity for therapeutic purposes. Among them, cannabidiol (CBD), a non-psychoactive component of cannabis, shows great promise for the treatment of psychosis, and is associated with fewer extrapyramidal side effects than conventional antipsychotic drugs. The overarching goal of this review is to provide current available knowledge on the role of the dopamine system and the ECS in schizophrenia, and to discuss key findings from animal studies and clinical trials investigating the antipsychotic potential of CBD.

#### **CONCLUSIONS:**

Microarray-based gene expression profiling demonstrated that CBD exerts its immunoregulatory effects in activated memory TMOG cells via (a) suppressing proinflammatory Th17-related transcription, (b) by promoting T cell exhaustion/tolerance, (c) enhancing IFN-dependent anti-proliferative program, (d) hampering antigen presentation, and (d) inducing antioxidant milieu resolving inflammation. These findings put forward mechanism by which CBD exerts its anti-inflammatory effects as well as explain the beneficial role of CBD in pathological memory T cells and in autoimmune diseases.

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### **Pathways and gene networks mediating the regulatory effects of cannabidiol, a nonpsychoactive cannabinoid, in autoimmune T cells.**

Kozela E, Juknat A, Gao F, Kaushansky N, Coppola G, Vogel Z.

#### **Abstract**

#### **BACKGROUND:**

Our previous studies showed that the non-psychoactive cannabinoid, cannabidiol (CBD), ameliorates the clinical symptoms in mouse myelin oligodendrocyte glycoprotein (MOG)35-55-induced experimental autoimmune encephalomyelitis model of multiple sclerosis (MS) as well as decreases the memory MOG35-55-specific T cell (TMOG) proliferation and cytokine secretion including IL-17, a key autoimmune factor. The mechanisms of these activities are currently poorly understood.

## METHODS:

Herein, using microarray-based gene expression profiling, we describe gene networks and intracellular pathways involved in CBD-induced suppression of these activated memory TMOG cells. Encephalitogenic TMOG cells were stimulated with MOG35-55 in the presence of spleen-derived antigen presenting cells (APC) with or without CBD. mRNA of purified TMOG was then subjected to Illumina microarray analysis followed by ingenuity pathway analysis (IPA), weighted gene co-expression network analysis (WGCNA) and gene ontology (GO) elucidation of gene interactions. Results were validated using qPCR and ELISA assays.

## RESULTS:

Gene profiling showed that the CBD treatment suppresses the transcription of a large number of proinflammatory genes in activated TMOG. These include cytokines (Xcl1, Il3, Il12a, Il1b), cytokine receptors (Cxcr1, Ifngr1), transcription factors (Ier3, Atf3, Nr4a3, Crem), and TNF superfamily signaling molecules (Tnfsf11, Tnfsf14, Tnfrsf9, Tnfrsf18). "IL-17 differentiation" and "IL-6 and IL-10-signaling" were identified among the top processes affected by CBD. CBD increases a number of IFN-dependent transcripts (Rgs16, Mx2, Rsad2, Irf4, Ifit2, Ephx1, Ets2) known to execute anti-proliferative activities in T cells. Interestingly, certain MOG35-55 up-regulated transcripts were maintained at high levels in the presence of CBD, including transcription factors (Egr2, Egr1, Tbx21), cytokines (Csf2, Tnf, Ifng), and chemokines (Ccl3, Ccl4, Cxcl10) suggesting that CBD may promote exhaustion of memory TMOG cells. In addition, CBD enhanced the transcription of T cell co-inhibitory molecules (Btla, Lag3, Trat1, and CD69) known to interfere with T/APC interactions. Furthermore, CBD enhanced the transcription of oxidative stress modulators with potent anti-inflammatory activity that are controlled by Nfe2l2/Nrf2 (Mt1, Mt2a, Slc30a1, Hmox1).

## CONCLUSIONS:

Microarray-based gene expression profiling demonstrated that CBD exerts its immunoregulatory effects in activated memory TMOG cells via (a) suppressing proinflammatory Th17-related transcription, (b) by promoting T cell exhaustion/tolerance, (c) enhancing IFN-dependent anti-proliferative program, (d) hampering antigen presentation, and (d) inducing antioxidant milieu resolving inflammation. These findings put forward mechanism by which CBD exerts its anti-inflammatory effects as well as explain the beneficial role of CBD in pathological memory T cells and in autoimmune diseases.

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Toxicol In Vitro. 2015 Dec 25;30(1 Pt B):231-40. doi: 10.1016/j.tiv.2015.11.004. Epub 2015 Nov 7.

**The neuroprotection of cannabidiol against MPP<sup>+</sup>-induced toxicity in PC12 cells involves trkA receptors, upregulation of axonal and synaptic proteins, neuritogenesis, and might be relevant to Parkinson's disease.**

Santos NA, Martins NM, Sisti FM, Fernandes LS, Ferreira RS, Queiroz RH, Santos AC.

## Abstract

Cannabidiol (CBD) is a non-psychoactive constituent of Cannabis sativa with potential to treat neurodegenerative diseases. Its neuroprotection has been mainly associated with anti-inflammatory and antioxidant events; however, other mechanisms might be involved. We investigated the involvement of neuritogenesis, NGF receptors (trkA), NGF, and neuronal proteins in the mechanism of neuroprotection of CBD against MPP(+) toxicity in PC12 cells.



CBD increased cell viability, differentiation, and the expression of axonal (GAP-43) and synaptic (synaptophysin and synapsin I) proteins. Its neurotogenic effect was not dependent or additive to NGF, but it was inhibited by K252a (trkA inhibitor). CBD did not increase the expression of NGF, but protected against its decrease induced by MPP(+), probably by an indirect mechanism. We also evaluated the neuritogenesis in SH-SY5Y cells, which do not express trkA receptors. CBD did not induce neuritogenesis in this cellular model, which supports the involvement of trkA receptors. This is the first study to report the involvement of neuronal proteins and trkA in the neuroprotection of CBD. Our findings suggest that CBD has a neurorestorative potential independent of NGF that might contribute to its neuroprotection against MPP(+), a neurotoxin relevant to Parkinson's disease.

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Daru. 2015 Oct 21;23:48. doi: 10.1186/s40199-015-0131-8.

### **A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis.**

Giacoppo S, Galuppo M, Pollastro F, Grassi G, Bramanti P, Mazzon E.

Abstract

#### **BACKGROUND:**

The present study was designed to investigate the efficacy of a new formulation of alone, purified cannabidiol (CBD) (>98 %), the main non-psychotropic cannabinoid of *Cannabis sativa*, as a topical treatment in an experimental model of autoimmune encephalomyelitis (EAE), the most commonly used model for multiple sclerosis (MS). Particularly, we evaluated whether administration of a topical 1 % CBD-cream, given at the time of symptomatic disease onset, could affect the EAE progression and if this treatment could also recover paralysis of hind limbs, qualifying topical-CBD for the symptomatic treatment of MS.

#### **METHODS:**

In order to have a preparation of 1 % of CBD-cream, pure CBD have been solubilized in propylene glycol and basic dense cream O/A. EAE was induced by immunization with myelin oligodendroglial glycoprotein peptide (MOG35-55) in C57BL/6 mice. After EAE onset, mice were allocated into several experimental groups (Naïve, EAE, EAE-1 % CBD-cream, EAE-vehicle cream, CTRL-1 % CBD-cream, CTRL-vehicle cream). Mice were observed daily for signs of EAE and weight loss. At the sacrifice of the animals, which occurred at the 28(th) day from EAE-induction, spinal cord and spleen tissues were collected in order to perform histological evaluation, immunohistochemistry and western blotting analysis.

#### **RESULTS:**

Achieved results surprisingly show that daily treatment with topical 1 % CBD-cream may exert neuroprotective effects against EAE, diminishing clinical disease score (mean of 5.0 in EAE mice vs 1.5 in EAE + CBD-cream), by recovering of paralysis of hind limbs and by ameliorating histological score typical of disease (lymphocytic infiltration and demyelination) in spinal cord tissues. Also, 1 % CBD-cream is able to counteract the EAE-induced damage reducing release of CD4 and CD8 $\alpha$  T cells (spleen tissue localization was quantified about 10,69 % and 35,96 % of positive staining respectively in EAE mice) and expression of the main pro-inflammatory cytokines as well as several other direct or indirect markers of inflammation (p-selectin, IL-10, GFAP, Foxp3, TGF- $\beta$ , IFN- $\gamma$ ), oxidative injury (Nitrotyrosine, iNOS, PARP) and apoptosis (Cleaved caspase 3).

## CONCLUSION:

All these data suggest an interesting new profile of CBD that could lead to its introduction in the clinical management of MS and its associated symptoms at least in association with current conventional therapy.

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Handb Exp Pharmacol. 2015;231:285-316. doi: 10.1007/978-3-319-20825-1\_10.

### **Cannabis and Endocannabinoid Signaling in Epilepsy.**

Katona I

#### Abstract

The antiepileptic potential of *Cannabis sativa* preparations has been historically recognized. Recent changes in legal restrictions and new well-documented cases reporting remarkably strong beneficial effects have triggered an upsurge in exploiting medical marijuana in patients with refractory epilepsy. Parallel research efforts in the last decade have uncovered the fundamental role of the endogenous cannabinoid system in controlling neuronal network excitability raising hopes for cannabinoid-based therapeutic approaches. However, emerging data show that patient responsiveness varies substantially, and that cannabis administration may sometimes even exacerbate seizures. Qualitative and quantitative chemical variability in cannabis products and personal differences in the etiology of seizures, or in the pathological reorganization of epileptic networks, can all contribute to divergent patient responses. Thus, the consensus view in the neurologist community is that drugs modifying the activity of the endocannabinoid system should first be tested in clinical trials to establish efficacy, safety, dosing, and proper indication in specific forms of epilepsies. To support translation from anecdote-based practice to evidence-based therapy, the present review first introduces current preclinical and clinical efforts for cannabinoid- or endocannabinoid-based epilepsy treatments. Next, recent advances in our knowledge of how endocannabinoid signaling limits abnormal network activity as a central component of the synaptic circuit-breaker system will be reviewed to provide a framework for the underlying neurobiological mechanisms of the beneficial and adverse effects. Finally, accumulating evidence demonstrating robust synapse-specific pathophysiological plasticity of endocannabinoid signaling in epileptic networks will be summarized to gain better understanding of how and when pharmacological interventions may have therapeutic relevance.

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PLoS One. 2014; 9(12): e113161.

### **Protective Effects of Cannabidiol on Lesion-Induced Intervertebral Disc Degeneration**

João W. Silveira, Ana Carolina Issy, Vitor A. Castania, Carlos E. G. Salmon, Marcello H. Nogueira-Barbosa, Francisco S. Guimarães, Helton L. A. Defino, and Elaine Del Bel.

Partha Mukhopadhyay, Editor

#### Abstract

Disc degeneration is a multifactorial process that involves hypoxia, inflammation, neoinnervation, accelerated catabolism, and reduction in water and glycosaminoglycan content.

Cannabidiol is the main non-psychoactive component of the *Cannabis sativa* with protective and anti-inflammatory properties. However, possible therapeutic effects of cannabidiol on intervertebral disc degeneration have not been investigated yet. The present study investigated the effects of cannabidiol intradiscal injection in the coccygeal intervertebral disc degeneration induced by the needle puncture model using magnetic resonance imaging (MRI) and histological analyses. Disc injury was induced in the tail of male Wistar rats via a single needle puncture. The discs selected for injury were punctured percutaneously using a 21-gauge needle. MRI and histological evaluation were employed to assess the results. The effects of intradiscal injection of cannabidiol (30, 60 or 120 nmol) injected immediately after lesion were analyzed acutely (2 days) by MRI. The experimental group that received cannabidiol 120 nmol was resubmitted to MRI examination and then to histological analyses 15 days after lesion/cannabidiol injection. The needle puncture produced a significant disc injury detected both by MRI and histological analyses. Cannabidiol significantly attenuated the effects of disc injury induced by the needle puncture. Considering that cannabidiol presents an extremely safe profile and is currently being used clinically, these results suggest that this compound could be useful in the treatment of intervertebral disc degeneration.

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Biochem Pharmacol. 2014 Nov 15;92(2):312-25. doi: 10.1016/j.bcp.2014.07.014. Epub 2014 Jul 25.

### **Cannabinoids increase lung cancer cell lysis by lymphokine-activated killer cells via upregulation of ICAM-1.**

Haustein M, Ramer R, Linnebacher M, Manda K, Hinz B.

#### **Abstract**

Cannabinoids have been shown to promote the expression of the intercellular adhesion molecule 1 (ICAM-1) on lung cancer cells as part of their anti-invasive and antimetastatic action. Using lung cancer cell lines (A549, H460) and metastatic cells derived from a lung cancer patient, the present study addressed the impact of cannabinoid-induced ICAM-1 on cancer cell adhesion to lymphokine-activated killer (LAK) cells and LAK cell-mediated cytotoxicity. Cannabidiol (CBD), a non-psychoactive cannabinoid, enhanced the susceptibility of cancer cells to adhere to and subsequently be lysed by LAK cells, with both effects being reversed by a neutralizing ICAM-1 antibody. Increased cancer cell lysis by CBD was likewise abrogated when CBD-induced ICAM-1 expression was blocked by specific siRNA or by antagonists to cannabinoid receptors (CB1, CB2) and to transient receptor potential vanilloid 1. In addition, enhanced killing of CBD-treated cancer cells was reversed by preincubation of LAK cells with an antibody to lymphocyte function associated antigen-1 (LFA-1) suggesting intercellular ICAM-1/LFA-1 crosslink as crucial event within this process. ICAM-1-dependent pro-killing effects were further confirmed for the phytocannabinoid  $\Delta(9)$ -tetrahydrocannabinol (THC) and R(+)-methanandamide (MA), a hydrolysis-stable endocannabinoid analogue. Finally, each cannabinoid elicited no significant increase of LAK cell-mediated lysis of non-tumor bronchial epithelial cells, BEAS-2B, associated with a far less pronounced (CBD, THC) or absent (MA) ICAM-1 induction as compared to cancer cells. Altogether, our data demonstrate cannabinoid-induced upregulation of ICAM-1 on lung cancer cells to be responsible for increased cancer cell lysis by LAK cells. These findings provide proof for a novel antitumorigenic mechanism of cannabinoids.

British Journal of Cancer (2006) 95, 197–203.

## **A pilot clinical study of $\Delta$ 9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme**

M Guzmán, M J Duarte, C Blázquez, J Ravina, M C Rosa, I Galve-Roperh, C Sánchez, G Velasco and L González-Feria

### **Abstract**

$\Delta$ 9-Tetrahydrocannabinol (THC) and other cannabinoids inhibit tumour growth and angiogenesis in animal models, so their potential application as antitumoral drugs has been suggested. However, the antitumoral effect of cannabinoids has never been tested in humans. Here we report the first clinical study aimed at assessing cannabinoid antitumoral action, specifically a pilot phase I trial in which nine patients with recurrent glioblastoma multiforme were administered THC intratumorally. The patients had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumour progression. The primary end point of the study was to determine the safety of intracranial THC administration. We also evaluated THC action on the length of survival and various tumour-cell parameters. A dose escalation regimen for THC administration was assessed. Cannabinoid delivery was safe and could be achieved without overt psychoactive effects. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% confidence interval: 15–33).  $\Delta$ 9-Tetrahydrocannabinol inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immunostaining when administered to two patients. The fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids.

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J Psychopharmacol. 2011 Jan;25(1):121-30. doi: 10.1177/0269881110379283. Epub 2010 Sep 9.

## **Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report.**

Crippa JA, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, Simões MV, Bhattacharyya S, Fusar-Poli P, Atakan Z, Santos Filho A, Freitas-Ferrari MC, McGuire PK, Zuardi AW, Busatto GF, Hallak JE.

### **Abstract**

Animal and human studies indicate that cannabidiol (CBD), a major constituent of cannabis, has anxiolytic properties. However, no study to date has investigated the effects of this compound on human pathological anxiety and its underlying brain mechanisms. The aim of the present study was to investigate this in patients with generalized social anxiety disorder (SAD) using functional neuroimaging. Regional cerebral blood flow (rCBF) at rest was measured twice using (99m)Tc-ECD SPECT in 10 treatment-naïve patients with SAD. In the first session, subjects were given an oral dose of CBD (400 mg) or placebo, in a double-blind procedure. In the second session, the same procedure was performed using the drug that had not been administered in the previous session. Within-subject between-condition rCBF comparisons were performed using statistical parametric mapping. Relative to placebo, CBD was associated with significantly decreased subjective anxiety ( $p < 0.001$ ), reduced ECD uptake in the left parahippocampal gyrus, hippocampus, and inferior temporal gyrus ( $p < 0.001$ , uncorrected), and increased ECD uptake in the right posterior cingulate gyrus

( $p < 0.001$ , uncorrected). These results suggest that CBD reduces anxiety in SAD and that this is related to its effects on activity in limbic and paralimbic brain areas.

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PLoS One. 2013 Nov 25;8(11):e80440. doi: 10.1371/journal.pone.0080440. eCollection 2013.

**Cannabinoid CB2 receptors regulate central sensitization and pain responses associated with osteoarthritis of the knee joint.**

Burston JJ, Sagar DR, Shao P, Bai M, King E, Brailsford L, Turner JM, Hathway GJ, Bennett AJ, Walsh DA, Kendall DA, Lichtman A, Chapman V.

**Abstract**

Osteoarthritis (OA) of the joint is a prevalent disease accompanied by chronic, debilitating pain. Recent clinical evidence has demonstrated that central sensitization contributes to OA pain. An improved understanding of how OA joint pathology impacts upon the central processing of pain is crucial for the identification of novel analgesic targets/new therapeutic strategies. Inhibitory cannabinoid 2 (CB2) receptors attenuate peripheral immune cell function and modulate central neuro-immune responses in models of neurodegeneration. Systemic administration of the CB2 receptor agonist JWH133 attenuated OA-induced pain behaviour, and the changes in circulating pro- and anti-inflammatory cytokines exhibited in this model. Electrophysiological studies revealed that spinal administration of JWH133 inhibited noxious-evoked responses of spinal neurones in the model of OA pain, but not in control rats, indicating a novel spinal role of this target. We further demonstrate dynamic changes in spinal CB2 receptor mRNA and protein expression in an OA pain model. The expression of CB2 receptor protein by both neurones and microglia in the spinal cord was significantly increased in the model of OA. Hallmarks of central sensitization, significant spinal astrogliosis and increases in activity of metalloproteases MMP-2 and MMP-9 in the spinal cord were evident in the model of OA pain. Systemic administration of JWH133 attenuated these markers of central sensitization, providing a neurobiological basis for analgesic effects of the CB2 receptor in this model of OA pain. Analysis of human spinal cord revealed a negative correlation between spinal cord CB2 receptor mRNA and macroscopic knee chondropathy. These data provide new clinically relevant evidence that joint damage and spinal CB2 receptor expression are correlated combined with converging pre-clinical evidence that activation of CB2 receptors inhibits central sensitization and its contribution to the manifestation of chronic OA pain. These findings suggest that targeting CB2 receptors may have therapeutic potential for treating OA pain.

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J Oral Facial Pain Headache. 2015 Winter;29(1):7-14. doi: 10.11607/ofph.1274.

**The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review.**

Boychuk DG, Goddard G, Mauro G, Orellana MF.

**Abstract**

## AIMS:

To carry out a systematic review to assess the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain.

## METHODS:

Electronic database searches were performed using Medline, PubMed, Embase, all evidence-based medicine reviews, and Web of Science, through communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), and by searching printed indices from 1950. Terms used were marijuana, marihuana, cannabis, cannabinoids, nabilone, delta-9-tetrahydrocannabinol, cannabidiol, ajulemic acid, dronabinol, pain, chronic, disease, and neuropathic. Randomized placebo-controlled trials (RCTs) involving cannabis and cannabinoids for the treatment of chronic nonmalignant pain were selected. Outcomes considered were reduction in pain intensity and adverse events.

## RESULTS:

Of the 24 studies that examined chronic neuropathic pain, 11 studies were excluded. The 13 included studies were rated using the Jadad Scale to measure bias in pain research. Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments.

## CONCLUSION:

Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess the impact of the duration of the treatment as well as the best form of drug delivery.

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Mult Scler. 2004 Aug;10(4):425-33.

### **An open-label pilot study of cannabis-based extracts for bladder dysfunction in advanced multiple sclerosis.**

Brady CM, DasGupta R, Dalton C, Wiseman OJ, Berkley KJ, Fowler CJ.

#### Abstract

The majority of patients with multiple sclerosis (MS) develop troublesome lower urinary tract symptoms (LUTS). Anecdotal reports suggest that cannabis may alleviate LUTS, and cannabinoid receptors in the bladder and nervous system are potential pharmacological targets. In an open trial we evaluated the safety, tolerability, dose range, and efficacy of two whole-plant extracts of *Cannabis sativa* in patients with advanced MS and refractory LUTS. Patients took extracts containing delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD; 2.5 mg of each per spray) for eight weeks followed by THC-only (2.5 mg THC per spray) for a further eight weeks, and then into a long-term extension. Assessments included urinary frequency and volume charts, incontinence pad weights, cystometry and visual analogue scales for secondary troublesome symptoms. Twenty-one patients were recruited and data from 15 were evaluated. Urinary urgency, the number and volume of incontinence episodes, frequency and nocturia all decreased significantly following treatment ( $P < 0.05$ , Wilcoxon's signed rank test). However, daily total voided, catheterized and urinary incontinence pad weights also decreased significantly on both extracts. Patient self-assessment of pain, spasticity and quality of sleep improved significantly ( $P < 0.05$ , Wilcoxon's signed rank test) with pain improvement continuing

up to median of 35 weeks. There were few troublesome side effects, suggesting that cannabis-based medicinal extracts are a safe and effective treatment for urinary and other problems in patients with advanced MS.

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Neuropharmacology. 2015 Feb;89:368-74. doi: 10.1016/j.neuropharm.2014.07.021. Epub 2014 Aug 11.

**Chronic cannabinoid receptor stimulation selectively prevents motor impairments in a mouse model of Huntington's disease.**

Pietropaolo S, Bellocchio L, Ruiz-Calvo A, Cabanas M, Du Z, Guzmán M, Garret M, Cho YH.

Abstract

Huntington's disease (HD) is a devastating neurodegenerative disease characterized by a progressive decline in motor abilities, as well as in cognitive and social behaviors. Most of these behavioral deficits are recapitulated in the R6/1 transgenic mouse, which can therefore be used as an experimental model to identify the neurobiological substrates of HD pathology and to design novel therapeutic approaches. The endocannabinoid system (ECS) is a relevant candidate to participate in the etiopathology of HD as it is a key modulator of brain function, especially in areas primarily affected by HD dysfunction such as the striatum. Thus, some studies have demonstrated an association between HD progression and alterations in the expression of several ECS elements, thereby suggesting that improving ECS function may constitute a useful strategy to eliminate or at least delay the appearance of HD symptoms. Here this hypothesis was specifically tested by evaluating whether the administration of a well-characterized cannabinoid receptor agonist (WIN 55,212), either acutely or chronically, improves the HD-like symptoms in R6/1 mice. While acute treatment did not change the behavioral phenotype of transgenic animals, chronic administration was able to prevent the appearance of motor deficits, to increase the number of striatal huntingtin inclusions and to prevent the loss of striatal medium-sized spiny neurons, without affecting the social or cognitive alterations. These findings suggest that prolonged administration of cannabinoid receptor agonists could be an appropriate strategy for selectively improving motor symptoms and stimulating neuroprotective processes in HD patients.

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da Silva, V.K., de Freitas, B.S., da Silva Dornelles, A. et al. Mol Neurobiol (2014) 49: 222. doi: 10.1007/s12035-013-8514-7

**Cannabidiol Normalizes Caspase 3, Synaptophysin, and Mitochondrial Fission Protein DNM1L Expression Levels in Rats with Brain Iron Overload: Implications for Neuroprotection**

Vanessa Kappel da SilvaBetânia Souza de FreitasArethusa da Silva DornellesLaura Roesler NeryLucio FalavignaRafael Dal Ponte FerreiraMaurício Reis BogoJaime Eduardo Cecílio HallakAntônio Waldo ZuardiJosé Alexandre S. CrippaNadja Schröder

Abstract

We have recently shown that chronic treatment with cannabidiol (CBD) was able to recover memory deficits induced by brain iron loading in a dose-dependent manner in rats. Brain iron

accumulation is implicated in the pathogenesis of neurodegenerative diseases, including Parkinson's and Alzheimer's, and has been related to cognitive deficits in animals and human subjects. Deficits in synaptic energy supply have been linked to neurodegenerative diseases, evidencing the key role played by mitochondria in maintaining viable neural cells and functional circuits. It has also been shown that brains of patients suffering from neurodegenerative diseases have increased expression of apoptosis-related proteins and specific DNA fragmentation. Here, we have analyzed the expression level of brain proteins involved with mitochondrial fusion and fission mechanisms (DNM1L and OPA1), the main integral transmembrane protein of synaptic vesicles (synaptophysin), and caspase 3, an apoptosis-related protein, to gain a better understanding of the potential of CBD in restoring the damage caused by iron loading in rats. We found that CBD rescued iron-induced effects, bringing hippocampal DNM1L, caspase 3, and synaptophysin levels back to values comparable to the control group. Our results suggest that iron affects mitochondrial dynamics, possibly triggering synaptic loss and apoptotic cell death and indicate that CBD should be considered as a potential molecule with memory-rescuing and neuroprotective properties to be used in the treatment of cognitive deficits observed in neurodegenerative disorders.

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Lancet. 2003 Nov 8;362(9395):1517-26.

**Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): multicentre randomised placebo-controlled trial.**

Zajicek J, Fox P, Sanders H, Wright D, Vickery J, Nunn A, Thompson A; UK MS Research Group.

Abstract

**BACKGROUND:**

Multiple sclerosis is associated with muscle stiffness, spasms, pain, and tremor. Much anecdotal evidence suggests that cannabinoids could help these symptoms. Our aim was to test the notion that cannabinoids have a beneficial effect on spasticity and other symptoms related to multiple sclerosis.

**METHODS:**

We did a randomised, placebo-controlled trial, to which we enrolled 667 patients with stable multiple sclerosis and muscle spasticity. 630 participants were treated at 33 UK centres with oral cannabis extract (n=211), Delta9-tetrahydrocannabinol (Delta9-THC; n=206), or placebo (n=213). Trial duration was 15 weeks. Our primary outcome measure was change in overall spasticity scores, using the Ashworth scale. Analysis was by intention to treat.

**FINDINGS:**

611 of 630 patients were followed up for the primary endpoint. We noted no treatment effect of cannabinoids on the primary outcome (p=0.40). The estimated difference in mean reduction in total Ashworth score for participants taking cannabis extract compared with placebo was 0.32 (95% CI -1.04 to 1.67), and for those taking Delta9-THC versus placebo it was 0.94 (-0.44 to 2.31). There was evidence of a treatment effect on patient-reported spasticity and pain (p=0.003), with improvement in spasticity reported in 61% (n=121, 95% CI 54.6-68.2), 60% (n=108, 52.5-66.8), and 46% (n=91, 39.0-52.9) of participants on cannabis extract, Delta9-THC, and placebo, respectively.



## INTERPRETATION:

Treatment with cannabinoids did not have a beneficial effect on spasticity when assessed with the Ashworth scale. However, though there was a degree of unmasking among the patients in the active treatment groups, objective improvement in mobility and patients' opinion of an improvement in pain suggest cannabinoids might be clinically useful.

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Eur J Pain. 2016 Jul;20(6):936-48. doi: 10.1002/ejp.818. Epub 2015 Oct 30.

### **Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis.**

Hammell DC, Zhang LP, Ma F, Abshire SM, McIlwrath SL, Stinchcomb AL, Westlund KN.

#### Abstract

#### BACKGROUND:

Current arthritis treatments often have side-effects attributable to active compounds as well as route of administration. Cannabidiol (CBD) attenuates inflammation and pain without side-effects, but CBD is hydrophobic and has poor oral bioavailability. Topical drug application avoids gastrointestinal administration, first pass metabolism, providing more constant plasma levels.

#### METHODS:

This study examined efficacy of transdermal CBD for reduction in inflammation and pain, assessing any adverse effects in a rat complete Freund's adjuvant-induced monoarthritic knee joint model. CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction. Joint circumference and immune cell invasion in histological sections were measured to indicate level of inflammation. Paw withdrawal latency (PWL) in response to noxious heat stimulation determined nociceptive sensitization, and exploratory behaviour ascertained animal's activity level.

#### RESULTS:

Measurement of plasma CBD concentration provided by transdermal absorption revealed linearity with 0.6-6.2 mg/day doses. Transdermal CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner. PWL recovered to near baseline level. Immunohistochemical analysis of spinal cord (CGRP, OX42) and dorsal root ganglia (TNF $\alpha$ ) revealed dose-dependent reductions of pro-inflammatory biomarkers. Results showed 6.2 and 62 mg/day were effective doses. Exploratory behaviour was not altered by CBD indicating limited effect on higher brain function.

## CONCLUSIONS:

These data indicate that topical CBD application has therapeutic potential for relief of arthritis pain-related behaviours and inflammation without evident side-effects.

Headache.

2015 Jun;55(6):885-916. doi: 10.1111/head.12570. Epub 2015 May 25.

## **Comprehensive Review of Medicinal Marijuana, Cannabinoids, and Therapeutic Implications in Medicine and Headache: What a Long Strange Trip It's Been ....**

Baron EP.

Abstract

## BACKGROUND:

The use of cannabis, or marijuana, for medicinal purposes is deeply rooted though history, dating back to ancient times. It once held a prominent position in the history of medicine, recommended by many eminent physicians for numerous diseases, particularly headache and migraine. Through the decades, this plant has taken a fascinating journey from a legal and frequently prescribed status to illegal, driven by political and social factors rather than by science. However, with an abundance of growing support for its multitude of medicinal uses, the misguided stigma of cannabis is fading, and there has been a dramatic push for legalizing medicinal cannabis and research. Almost half of the United States has now legalized medicinal cannabis, several states have legalized recreational use, and others have legalized cannabidiol-only use, which is one of many therapeutic cannabinoids extracted from cannabis. Physicians need to be educated on the history, pharmacology, clinical indications, and proper clinical use of cannabis, as patients will inevitably inquire about it for many diseases, including chronic pain and headache disorders for which there is some intriguing supportive evidence.

## OBJECTIVE:

To review the history of medicinal cannabis use, discuss the pharmacology and physiology of the endocannabinoid system and cannabis-derived cannabinoids, perform a comprehensive literature review of the clinical uses of medicinal cannabis and cannabinoids with a focus on migraine and other headache disorders, and outline general clinical practice guidelines.

## CONCLUSION:

The literature suggests that the medicinal use of cannabis may have a therapeutic role for a multitude of diseases, particularly chronic pain disorders including headache. Supporting literature suggests a role for medicinal cannabis and cannabinoids in several types of headache disorders including migraine and cluster headache, although it is primarily limited to case based, anecdotal, or laboratory-based scientific research. Cannabis contains an extensive number of pharmacological and biochemical compounds, of which only a minority are understood, so many potential therapeutic uses likely remain undiscovered. Cannabinoids appear to modulate and interact at many pathways inherent to migraine, triptan mechanisms of action, and opiate pathways, suggesting potential synergistic or similar benefits. Modulation of the endocannabinoid system through agonism or antagonism of its receptors, targeting its metabolic pathways, or combining cannabinoids with other analgesics for synergistic effects, may provide the foundation for many new classes of medications. Despite the limited evidence and research suggesting a role for cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation.

J Oral Facial Pain Headache. 2015 Winter;29(1):7-14. doi: 10.11607/ofph.1274.

**The effectiveness of cannabinoids in the management of chronic nonmalignant neuropathic pain: a systematic review.**

Boychuk DG, Goddard G, Mauro G, Orellana MF.

Abstract

AIMS:

To carry out a systematic review to assess the effectiveness of cannabis extracts and cannabinoids in the management of chronic nonmalignant neuropathic pain.

METHODS:

Electronic database searches were performed using Medline, PubMed, Embase, all evidence-based medicine reviews, and Web of Science, through communication with the Canadian Consortium for the Investigation of Cannabinoids (CCIC), and by searching printed indices from 1950. Terms used were marijuana, marihuana, cannabis, cannabinoids, nabilone, delta- 9-tetrahydrocannabinol, cannabidiol, ajulemic acid, dronabinol, pain, chronic, disease, and neuropathic. Randomized placebo-controlled trials (RCTs) involving cannabis and cannabinoids for the treatment of chronic nonmalignant pain were selected. Outcomes considered were reduction in pain intensity and adverse events.

RESULTS:

Of the 24 studies that examined chronic neuropathic pain, 11 studies were excluded. The 13 included studies were rated using the Jadad Scale to measure bias in pain research. Evaluation of these studies suggested that cannabinoids may provide effective analgesia in chronic neuropathic pain conditions that are refractory to other treatments.

CONCLUSION:

Cannabis-based medicinal extracts used in different populations of chronic nonmalignant neuropathic pain patients may provide effective analgesia in conditions that are refractory to other treatments. Further high-quality studies are needed to assess the impact of the duration of the treatment as well as the best form of drug delivery.

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Eur Neurol. 2014;72 Suppl 1:6-8. doi: 10.1159/000367615. Epub 2014 Sep 26.

**Advances in the management of multiple sclerosis spasticity: multiple sclerosis spasticity nervous pathways.**

Centonze D.

Abstract

## BACKGROUND:

Spasticity arises from hyperexcitability of the neural stretch reflex arc secondary to injury of the corticospinal tract. In response to injury, the density of glutamatergic inputs from afferent 1A fibers to motor neurons increases dramatically and adaptive changes occur in the morphology of microglia cells in the spinal cord.

## SUMMARY:

Involvement of the endocannabinoid system in pathophysiological mechanisms responsible for spasticity has been demonstrated in animal models of MS. Stimulation of cannabinoid (CB)1 receptors reduces the hyperglutamatergic drive from sensory afferents to spinal cord motor neurons and blocks the synaptic effects of activated microglia and pro-inflammatory mediators (e.g. TNF- $\alpha$ ) on glutamatergic transmission. Enhancing corticospinal tract excitability through intermittent theta burst stimulation inhibits the stretch reflex and spasticity by promoting long-term potentiation, a form of synaptic plasticity that requires stimulation of CB1 receptors. Evidence indicates that the antispasticity effects of THC:CBD oromucosal spray (Sativex®) are associated with enhanced cortical long-term potentiation. Key Messages: Glutamatergic and GABAergic pathways are involved in the regulation of muscle tone. CB1 receptors, which are associated with movement, postural control, and pain and sensory perception, influence glutamatergic pathways. THC:CBD oromucosal spray was shown to reverse motor cortex plasticity from long-term depression through long-term potentiation of synaptic transmission, thereby restoring, at least in part, effective corticospinal inputs to spinal circuits.

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J Pharmacol Exp Ther. 2014 Nov;351(2):457-66. doi: 10.1124/jpet.114.217125. Epub 2014 Sep 11.

### **Cannabidiol improves vasorelaxation in Zucker diabetic fatty rats through cyclooxygenase activation.**

Wheal AJ, Cipriano M, Fowler CJ, Randall MD, O'Sullivan SE.

#### Abstract

Cannabidiol (CBD) decreases insulinitis, inflammation, neuropathic pain, and myocardial dysfunction in preclinical models of diabetes. We recently showed that CBD also improves vasorelaxation in the Zucker diabetic fatty (ZDF) rat, and the objective of the present study was to establish the mechanisms underlying this effect. Femoral arteries from ZDF rats and ZDF lean controls were isolated, mounted on a myograph, and incubated with CBD (10  $\mu$ M) or vehicle for 2 hours. Subsequent vasorelaxant responses were measured in combination with various interventions. Prostaglandin metabolites were detected using enzyme immunoassay. Direct effects of CBD on cyclooxygenase (COX) enzyme activity were measured by oxygraph assay. CBD enhanced the maximum vasorelaxation to acetylcholine (ACh) in femoral arteries from ZDF lean rats ( $P < 0.01$ ) and especially ZDF rats ( $P < 0.0001$ ). In ZDF arteries, this enhancement persisted after cannabinoid receptor (CB) type 1, endothelial CB, or peroxisome proliferator-activated receptor- $\gamma$  antagonism but was inhibited by CB2 receptor antagonism. CBD also uncovered a vasorelaxant response to a CB2 agonist not previously observed. The CBD-enhanced ACh response was endothelium-, nitric oxide-, and hydrogen peroxide-independent. It was, however, COX-1/2- and superoxide dismutase-dependent, and CBD enhanced the activity of both purified COX-1 and COX-2. The CBD-enhanced ACh response in the arteries was inhibited by a prostanoid EP4 receptor antagonist. Prostaglandin E2 metabolite levels were below the limits of detection, but 6-keto prostaglandin F1  $\alpha$  was decreased after

CBD incubation. These data show that CBD exposure enhances the ability of arteries to relax via enhanced production of vasodilator COX-1/2-derived products acting at EP4 receptors.

Rambam Maimonides Med J. 2013 Oct 29;4(4):e0022. doi: 10.5041/RMMJ.10129. eCollection 2013.

### **The endocannabinoid system, cannabinoids, and pain.**

Fine PG, Rosenfeld MJ.

#### **Abstract**

The endocannabinoid system is involved in a host of homeostatic and physiologic functions, including modulation of pain and inflammation. The specific roles of currently identified endocannabinoids that act as ligands at endogenous cannabinoid receptors within the central nervous system (primarily but not exclusively CB 1 receptors) and in the periphery (primarily but not exclusively CB 2 receptors) are only partially elucidated, but they do exert an influence on nociception. Exogenous plant-based cannabinoids (phytocannabinoids) and chemically related compounds, like the terpenes, commonly found in many foods, have been found to exert significant analgesic effects in various chronic pain conditions. Currently, the use of  $\Delta^9$ -tetrahydrocannabinol is limited by its psychoactive effects and predominant delivery route (smoking), as well as regulatory or legal constraints. However, other phytocannabinoids in combination, especially cannabidiol and  $\beta$ -caryophyllene, delivered by the oral route appear to be promising candidates for the treatment of chronic pain due to their high safety and low adverse effects profiles. This review will provide the reader with the foundational basic and clinical science linking the endocannabinoid system and the phytocannabinoids with their potentially therapeutic role in the management of chronic pain.

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Br J Pharmacol. 2014 Feb;171(3):636-45. doi: 10.1111/bph.12439.

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

Ward SJ, McAllister SD, Kawamura R, Murase R, Neelakantan H, Walker EA.

#### **Abstract**

##### **BACKGROUND AND PURPOSE:**

Paclitaxel (PAC) is associated with chemotherapy-induced neuropathic pain (CIPN) that can lead to the cessation of treatment in cancer patients even in the absence of alternate therapies. We previously reported that chronic administration of the non-psychoactive cannabinoid cannabidiol (CBD) prevents PAC-induced mechanical and thermal sensitivity in mice. Hence, we sought to determine receptor mechanisms by which CBD inhibits CIPN and whether CBD negatively effects nervous system function or chemotherapy efficacy.

##### **EXPERIMENTAL APPROACH:**

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

## KEY RESULTS:

PAC-induced mechanical sensitivity was prevented by administration of CBD (2.5 - 10 mg·kg<sup>-1</sup>) in female C57Bl/6 mice. This effect was reversed by co-administration of the 5-HT(1A) antagonist WAY 100635, but not the CB<sub>1</sub> antagonist SR141716 or the CB<sub>2</sub> antagonist SR144528. CBD produced no conditioned rewarding effects and did not affect conditioned learning and memory. Also, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability.

## CONCLUSIONS AND IMPLICATIONS:

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

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J Immunotoxicol. 2013 Jul-Sep;10(3):321-8. doi: 10.3109/1547691X.2012.741628. Epub 2012 Nov 23.

### **Cannabidiol (CBD) enhances lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice.**

Karmaus PW, Wagner JG, Harkema JR, Kaminski NE, Kaplan BL.

#### Abstract

Cannabidiol (CBD) is a plant-derived cannabinoid that has been predominantly characterized as anti-inflammatory. However, it is clear that immune effects of cannabinoids can vary with cannabinoid concentration, or type or magnitude of immune stimulus. The present studies demonstrate that oral administration of CBD enhanced lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice. The enhanced inflammatory cell infiltrate as observed in bronchoalveolar lavage fluid (BALF) was comprised mainly of neutrophils, with some monocytes. Concomitantly, CBD enhanced pro-inflammatory cytokine mRNA production, including tumor necrosis factor- $\alpha$  (Tnfa), interleukins (IL)-5 and -23 (Il6, Il23), and granulocyte colony stimulating factor (Gcsf). These results demonstrate that the CBD-mediated enhancement of LPS-induced pulmonary inflammation is mediated at the level of transcription of a variety of pro-inflammatory genes. The significance of these studies is that CBD is part of a therapeutic currently in use for spasticity and pain in multiple sclerosis patients, and therefore it is important to further understand mechanisms by which CBD alters immune function.

Cell Death Dis. 2012 Jun 28;3:e331. doi: 10.1038/cddis.2012.71.

**Cannabidiol protects oligodendrocyte progenitor cells from inflammation-induced apoptosis by attenuating endoplasmic reticulum stress.**

Mecha M1, Torrao AS, Mestre L, Carrillo-Salinas FJ, Mechoulam R, Guaza C.

**Abstract**

Cannabidiol (CBD) is the most abundant cannabinoid in *Cannabis sativa* that has no psychoactive properties. CBD has been approved to treat inflammation, pain and spasticity associated with multiple sclerosis (MS), of which demyelination and oligodendrocyte loss are hallmarks. Thus, we investigated the protective effects of CBD against the damage to oligodendrocyte progenitor cells (OPCs) mediated by the immune system. Doses of 1  $\mu$ M CBD protect OPCs from oxidative stress by decreasing the production of reactive oxygen species. CBD also protects OPCs from apoptosis induced by LPS/IFN $\gamma$  through the decrease of caspase 3 induction via mechanisms that do not involve CB1, CB2, TRPV1 or PPAR $\gamma$  receptors. Tunicamycin-induced OPC death was attenuated by CBD, suggesting a role of endoplasmic reticulum (ER) stress in the mode of action of CBD. This protection against ER stress-induced apoptosis was associated with reduced phosphorylation of eIF2 $\alpha$ , one of the initiators of the ER stress pathway. Indeed, CBD diminished the phosphorylation of PKR and eIF2 $\alpha$  induced by LPS/IFN $\gamma$ . The pro-survival effects of CBD in OPCs were accompanied by decreases in the expression of ER apoptotic effectors (CHOP, Bax and caspase 12), and increased expression of the anti-apoptotic Bcl-2. These findings suggest that attenuation of the ER stress pathway is involved in the 'oligoprotective' effects of CBD during inflammation.

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Pharmaceuticals (Basel). 2012 May 21;5(5):529-52. doi: 10.3390/ph5050529.

**Cannabidiol in humans-the quest for therapeutic targets.**

Zhornitsky S, Potvin S.

**Abstract**

Cannabidiol (CBD), a major phytocannabinoid constituent of cannabis, is attracting growing attention in medicine for its anxiolytic, antipsychotic, antiemetic and anti-inflammatory properties. However, up to this point, a comprehensive literature review of the effects of CBD in humans is lacking. The aim of the present systematic review is to examine the randomized and crossover studies that administered CBD to healthy controls and to clinical patients. A systematic search was performed in the electronic databases PubMed and EMBASE using the key word "cannabidiol". Both monotherapy and combination studies (e.g., CBD +  $\Delta$ 9-THC) were included. A total of 34 studies were identified: 16 of these were experimental studies, conducted in healthy subjects, and 18 were conducted in clinical populations, including multiple sclerosis (six studies), schizophrenia and bipolar mania (four studies), social anxiety disorder (two studies), neuropathic and cancer pain (two studies), cancer anorexia (one study), Huntington's disease (one study), insomnia (one study), and epilepsy (one study). Experimental studies indicate that a high-dose of inhaled/intravenous CBD is required to inhibit the effects of a lower dose of  $\Delta$ 9-THC. Moreover, some experimental and clinical studies suggest that oral/oromucosal CBD may prolong and/or intensify  $\Delta$ 9-THC-induced effects, whereas others suggest that it may inhibit  $\Delta$ 9-THC-induced effects. Finally, preliminary clinical trials suggest that high-dose oral CBD (150-600 mg/d) may exert a therapeutic effect for social anxiety disorder, insomnia and epilepsy, but also that it may cause mental sedation. Potential pharmacokinetic and pharmacodynamic explanations for these results are discussed.

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Free Radic Biol Med. 2011 Sep 1;51(5):1054-61. doi: 10.1016/j.freeradbiomed.2011.01.007. Epub 2011 Jan 14.

**Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress.**

Booz GW.

**Abstract**

Oxidative stress with reactive oxygen species generation is a key weapon in the arsenal of the immune system for fighting invading pathogens and initiating tissue repair. If excessive or unresolved, however, immune-related oxidative stress can initiate further increasing levels of oxidative stress that cause organ damage and dysfunction. Targeting oxidative stress in various diseases therapeutically has proven more problematic than first anticipated given the complexities and perversity of both the underlying disease and the immune response. However, growing evidence suggests that the endocannabinoid system, which includes the CB<sub>1</sub> and CB<sub>2</sub> G-protein-coupled receptors and their endogenous lipid ligands, may be an area that is ripe for therapeutic exploitation. In this context, the related nonpsychotropic cannabinoid cannabidiol, which may interact with the endocannabinoid system but has actions that are distinct, offers promise as a prototype for anti-inflammatory drug development. This review discusses recent studies suggesting that cannabidiol may have utility in treating a number of human diseases and disorders now known to involve activation of the immune system and associated oxidative stress, as a contributor to their etiology and progression. These include rheumatoid arthritis, types 1 and 2 diabetes, atherosclerosis, Alzheimer disease, hypertension, the metabolic syndrome, ischemia-reperfusion injury, depression, and neuropathic pain.

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Trends Pharmacol Sci. 2009 Oct;30(10):515-27. doi: 10.1016/j.tips.2009.07.006. Epub 2009 Sep 2.

**Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb.**

Izzo AA1, Borrelli F, Capasso R, Di Marzo V, Mechoulam R.

**Abstract**

Delta(9)-tetrahydrocannabinol binds cannabinoid (CB(1) and CB(2)) receptors, which are activated by endogenous compounds (endocannabinoids) and are involved in a wide range of physiopathological processes (e.g. modulation of neurotransmitter release, regulation of pain perception, and of cardiovascular, gastrointestinal and liver functions). The well-known psychotropic effects of Delta(9)-tetrahydrocannabinol, which are mediated by activation of brain CB(1) receptors, have greatly limited its clinical use. However, the plant Cannabis contains many cannabinoids with weak or no psychoactivity that, therapeutically, might be more promising than Delta(9)-tetrahydrocannabinol. Here, we provide an overview of the recent pharmacological advances, novel mechanisms of action, and potential therapeutic applications of such non-psychotropic plant-derived cannabinoids. Special emphasis is given to cannabidiol, the possible applications of which have recently emerged in inflammation, diabetes, cancer,



affective and neurodegenerative diseases, and to Delta(9)-tetrahydrocannabivarin, a novel CB(1) antagonist which exerts potentially useful actions in the treatment of epilepsy and obesity.

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Curr Neuropharmacol. 2006 Jul;4(3):239-57.

**Role of the cannabinoid system in pain control and therapeutic implications for the management of acute and chronic pain episodes.**

Manzanares J, Julian M, Carrascosa A.

**Abstract**

Cannabis extracts and synthetic cannabinoids are still widely considered illegal substances. Preclinical and clinical studies have suggested that they may result useful to treat diverse diseases, including those related with acute or chronic pain. The discovery of cannabinoid receptors, their endogenous ligands, and the machinery for the synthesis, transport, and degradation of these retrograde messengers, has equipped us with neurochemical tools for novel drug design. Agonist-activated cannabinoid receptors, modulate nociceptive thresholds, inhibit release of pro-inflammatory molecules, and display synergistic effects with other systems that influence analgesia, especially the endogenous opioid system. Cannabinoid receptor agonists have shown therapeutic value against inflammatory and neuropathic pains, conditions that are often refractory to therapy. Although the psychoactive effects of these substances have limited clinical progress to study cannabinoid actions in pain mechanisms, preclinical research is progressing rapidly. For example, CB(1)-mediated suppression of mast cell activation responses, CB(2)-mediated indirect stimulation of opioid receptors located in primary afferent pathways, and the discovery of inhibitors for either the transporters or the enzymes degrading endocannabinoids, are recent findings that suggest new therapeutic approaches to avoid central nervous system side effects. In this review, we will examine promising indications of cannabinoid receptor agonists to alleviate acute and chronic pain episodes. Recently, Cannabis sativa extracts, containing known doses of tetrahydrocannabinol and cannabidiol, have granted approval in Canada for the relief of neuropathic pain in multiple sclerosis. Further double-blind placebo-controlled clinical trials are needed to evaluate the potential therapeutic effectiveness of various cannabinoid agonists-based medications for controlling different types of pain.

J Pharmacol Exp Ther. 2010 Feb;332(2):569-77. doi: 10.1124/jpet.109.159145. Epub 2009 Nov 11.

**Cannabidiol displays antiepileptiform and antiseizure properties in vitro and in vivo.**

Jones NA, Hill AJ, Smith I, Bevan SA, Williams CM, Whalley BJ, Stephens GJ.

**Abstract**

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

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Neuropharmacology, Volume 103, April 2016, Pages 16–26

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

Raquel Lingea, Laura Jiménez-Sánchez<sup>b</sup>, Leticia Campa<sup>b</sup>, Fuencisla Pilar-Cuéllara, Rebeca Vidala, Angel Pazosa, Albert Adella, Álvaro Díaz, <sup>b</sup>,

**Abstract**

Cannabidiol (CBD), the main non-psychotomimetic component of marijuana, exhibits anxiolytic-like properties in many behavioural tests, although its potential for treating major depression has been poorly explored. Moreover, the mechanism of action of CBD remains unclear. Herein, we have evaluated the effects of CBD following acute and chronic administration in the olfactory bulbectomy mouse model of depression (OBX), and investigated the underlying mechanism. For this purpose, we conducted behavioural (open field and sucrose preference tests) and neurochemical (microdialysis and autoradiography of 5-HT1A receptor functionality) studies following treatment with CBD. We also assayed the pharmacological antagonism of the effects of CBD to dissect out the mechanism of action. Our results demonstrate that CBD exerts fast and maintained antidepressant-like effects as evidenced by the reversal of the OBX-induced hyperactivity and anhedonia. In vivo microdialysis revealed that the administration of CBD significantly enhanced serotonin and glutamate levels in vmPFCx in a different manner depending on the emotional state and the duration of the treatment. The potentiating effect upon neurotransmitters levels occurring immediately after the first injection of CBD might underlie the fast antidepressant-like actions in OBX mice. Both antidepressant-like effect and enhanced cortical 5-HT/glutamate neurotransmission induced by CBD were prevented by 5-HT1A receptor blockade. Moreover, adaptive changes in pre- and post-synaptic 5-HT1A receptor functionality were also found after chronic CBD. In conclusion, our findings indicate that CBD could

represent a novel fast antidepressant drug, via enhancing both serotonergic and glutamate cortical signalling through a 5-HT<sub>1A</sub> receptor-dependent mechanism.

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CNS & neurological disorders drug targets 13(6):953-60. August 2014

### **Antidepressant-Like and Anxiolytic-Like Effects of Cannabidiol: A Chemical Compound of Cannabis sativa**

Alexandre Rafael de Mello Schier, Natalia Pinho de Oliveira Ribeiro, Danielle Sousa Coutinho, Adriana Cardoso

#### **Abstract**

Anxiety and depression are pathologies that affect human beings in many aspects of life, including social life, productivity and health. Cannabidiol (CBD) is a constituent non-psychotomimetic of Cannabis sativa with great psychiatric potential, including uses as an antidepressant-like and anxiolytic-like compound. The aim of this work is to review the animal study articles using CBD as an anxiolytic-like and antidepressant-like compound. Articles were identified using the major electronic databases, including the ISI Web of Knowledge, Scielo, PubMed and PsycINFO, combining the terms “cannabidiol”, “antidepressant-like” and “anxiolytic-like”. As languages for this search, we used Portuguese and English. Animal study articles were primarily included. Studies involving animal models, performing a variety of experiments on the above-mentioned disorders, such as the forced swimming test (FST), elevated plus maze (EPM) and Vogel conflict test (VCT), suggest that CBD exhibited an anti-anxiety and anti-depressant effects in animal models discussed. Experiments with CBD demonstrated non-activation of neuro-receptors CB<sub>1</sub> and CB<sub>2</sub>. Most of the studies demonstrated a good interaction between CBD and the 5-HT<sub>1A</sub> neuro-receptor, except by on that it was not clear.

Br J Pharmacol. 2011 Aug;163(7):1411-22. doi: 10.1111/j.1476-5381.2010.01176.x.

### **Regulation of nausea and vomiting by cannabinoids.**

Parker LA, Rock EM, Limebeer CL.

#### **Abstract**

Considerable evidence demonstrates that manipulation of the endocannabinoid system regulates nausea and vomiting in humans and other animals. The anti-emetic effect of cannabinoids has been shown across a wide variety of animals that are capable of vomiting in response to a toxic challenge. CB<sub>1</sub> agonism suppresses vomiting, which is reversed by CB<sub>1</sub> antagonism, and CB<sub>1</sub> inverse agonism promotes vomiting. Recently, evidence from animal experiments suggests that cannabinoids may be especially useful in treating the more difficult to control symptoms of nausea and anticipatory nausea in chemotherapy patients, which are less well controlled by the currently available conventional pharmaceutical agents. Although rats and mice are incapable of vomiting, they display a distinctive conditioned gaping response when re-exposed to cues (flavours or contexts) paired with a nauseating treatment. Cannabinoid agonists ( $\Delta^9$ -THC, HU-210) and the fatty acid amide hydrolase (FAAH) inhibitor, URB-597,

suppress conditioned gaping reactions (nausea) in rats as they suppress vomiting in emetic species. Inverse agonists, but not neutral antagonists, of the CB(1) receptor promote nausea, and at subthreshold doses potentiate nausea produced by other toxins (LiCl). The primary non-psychoactive compound in cannabis, cannabidiol (CBD), also suppresses nausea and vomiting within a limited dose range. The anti-nausea/anti-emetic effects of CBD may be mediated by indirect activation of somatodendritic 5-HT(1A) receptors in the dorsal raphe nucleus; activation of these autoreceptors reduces the release of 5-HT in terminal forebrain regions. Preclinical research indicates that cannabinoids, including CBD, may be effective clinically for treating both nausea and vomiting produced by chemotherapy or other therapeutic treatments.

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Br J Clin Pharmacol. 2013 Feb;75(2):323-33. doi: 10.1111/j.1365-2125.2012.04341.x.

### **Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?**

Fernández-Ruiz J, Sagredo O, Pazos MR, García C, Pertwee R, Mechoulam R, Martínez-Orgado J.

#### **Abstract**

Cannabidiol (CBD) is a phytocannabinoid with therapeutic properties for numerous disorders exerted through molecular mechanisms that are yet to be completely identified. CBD acts in some experimental models as an anti-inflammatory, anticonvulsant, anti-oxidant, anti-emetic, anxiolytic and antipsychotic agent, and is therefore a potential medicine for the treatment of neuroinflammation, epilepsy, oxidative injury, vomiting and nausea, anxiety and schizophrenia, respectively. The neuroprotective potential of CBD, based on the combination of its anti-inflammatory and anti-oxidant properties, is of particular interest and is presently under intense preclinical research in numerous neurodegenerative disorders. In fact, CBD combined with  $\Delta(9)$ -tetrahydrocannabinol is already under clinical evaluation in patients with Huntington's disease to determine its potential as a disease-modifying therapy. The neuroprotective properties of CBD do not appear to be exerted by the activation of key targets within the endocannabinoid system for plant-derived cannabinoids like  $\Delta(9)$ -tetrahydrocannabinol, i.e. CB(1) and CB(2) receptors, as CBD has negligible activity at these cannabinoid receptors, although certain activity at the CB(2) receptor has been documented in specific pathological conditions (i.e. damage of immature brain). Within the endocannabinoid system, CBD has been shown to have an inhibitory effect on the inactivation of endocannabinoids (i.e. inhibition of FAAH enzyme), thereby enhancing the action of these endogenous molecules on cannabinoid receptors, which is also noted in certain pathological conditions. CBD acts not only through the endocannabinoid system, but also causes direct or indirect activation of metabotropic receptors for serotonin or adenosine, and can target nuclear receptors of the PPAR family and also ion channels.

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Eur J Pharmacol. Author manuscript; available in PMC 2015 Jan 5.

### **Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system**

Keith A. Sharkey, Nissar A. Darmani, and Linda A. Parker

## Abstract

Nausea and vomiting (emesis) are important elements in defensive or protective responses that animals use to avoid ingestion or digestion of potentially harmful substances. However, these neurally-mediated responses are at times manifested as symptoms of disease and they are frequently observed as side-effects of a variety of medications, notably those used to treat cancer. Cannabis has long been known to limit or prevent nausea and vomiting from a variety of causes. This has led to extensive investigations that have revealed an important role for cannabinoids and their receptors in the regulation of nausea and emesis. With the discovery of the endocannabinoid system, novel ways to regulate both nausea and vomiting have been discovered that involve the production of endogenous cannabinoids acting centrally. Here we review recent progress in understanding the regulation of nausea and vomiting by cannabinoids and the endocannabinoid system, and we discuss the potential to utilize the endocannabinoid system in the treatment of these frequently debilitating conditions.

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Int J Mol Sci. 2016 Feb; 17(2): 230.

### **Endocannabinoids as Guardians of Metastasis**

Irmgard Tegeder, Xiaofeng Jia, Academic Editor

#### Abstract

Endocannabinoids including anandamide and 2-arachidonoylglycerol are involved in cancer pathophysiology in several ways, including tumor growth and progression, peritumoral inflammation, nausea and cancer pain. Recently we showed that the endocannabinoid profiles are deranged during cancer to an extent that this manifests in alterations of plasma endocannabinoids in cancer patients, which was mimicked by similar changes in rodent models of local and metastatic cancer. The present topical review summarizes the complexity of endocannabinoid signaling in the context of tumor growth and metastasis.

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Br J Pharmacol. 2011 Aug;163(7):1411-22. doi: 10.1111/j.1476-5381.2010.01176.x.

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Parker LA, Rock EM, Limebeer CL.

#### Abstract

Considerable evidence demonstrates that manipulation of the endocannabinoid system regulates nausea and vomiting in humans and other animals. The anti-emetic effect of cannabinoids has been shown across a wide variety of animals that are capable of vomiting in response to a toxic challenge. CB(1) agonism suppresses vomiting, which is reversed by CB(1) antagonism, and CB(1) inverse agonism promotes vomiting. Recently, evidence from animal experiments suggests that cannabinoids may be especially useful in treating the more difficult to control symptoms of nausea and anticipatory nausea in chemotherapy patients, which are less well controlled by the currently available conventional pharmaceutical agents. Although rats and

mice are incapable of vomiting, they display a distinctive conditioned gaping response when re-exposed to cues (flavours or contexts) paired with a nauseating treatment. Cannabinoid agonists ( $\Delta(9)$ -THC, HU-210) and the fatty acid amide hydrolase (FAAH) inhibitor, URB-597, suppress conditioned gaping reactions (nausea) in rats as they suppress vomiting in emetic species. Inverse agonists, but not neutral antagonists, of the CB(1) receptor promote nausea, and at subthreshold doses potentiate nausea produced by other toxins (LiCl). The primary non-psychoactive compound in cannabis, cannabidiol (CBD), also suppresses nausea and vomiting within a limited dose range. The anti-nausea/anti-emetic effects of CBD may be mediated by indirect activation of somatodendritic 5-HT(1A) receptors in the dorsal raphe nucleus; activation of these autoreceptors reduces the release of 5-HT in terminal forebrain regions. Preclinical research indicates that cannabinoids, including CBD, may be effective clinically for treating both nausea and vomiting produced by chemotherapy or other therapeutic treatments.

AAPS J. 2009 Mar; 11(1): 109.

### **Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation**

Sumner H. Burstein corresponding author and Robert B. Zurier

#### **Abstract**

This review covers reports published in the last 5 years on the anti-inflammatory activities of all classes of cannabinoids, including phytocannabinoids such as tetrahydrocannabinol and cannabidiol, synthetic analogs such as ajulemic acid and nabilone, the endogenous cannabinoids anandamide and related compounds, namely, the elmiric acids, and finally, noncannabinoid components of Cannabis that show anti-inflammatory action. It is intended to be an update on the topic of the involvement of cannabinoids in the process of inflammation. A possible mechanism for these actions is suggested involving increased production of eicosanoids that promote the resolution of inflammation. This differentiates these cannabinoids from cyclooxygenase-2 inhibitors that suppress the synthesis of eicosanoids that promote the induction of the inflammatory process.

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J Biol Chem. 2010 Jan 15;285(3):1616-26. doi: 10.1074/jbc.M109.069294. Epub 2009 Nov 12.

### **Cannabinoids Delta(9)-tetrahydrocannabinol and cannabidiol differentially inhibit the lipopolysaccharide-activated NF-kappaB and interferon-beta/STAT proinflammatory pathways in BV-2 microglial cells.**

Kozela E1, Pietr M, Juknat A, Rimmerman N, Levy R, Vogel Z.

#### **Abstract**

Cannabinoids have been shown to exert anti-inflammatory activities in various in vivo and in vitro experimental models as well as ameliorate various inflammatory degenerative diseases. However, the mechanisms of these effects are not completely understood. Using the BV-2 mouse microglial cell line and lipopolysaccharide (LPS) to induce an inflammatory response, we studied the signaling pathways engaged in the anti-inflammatory effects of cannabinoids as well as their influence on the expression of several genes known to be involved in inflammation. We found that the two major cannabinoids present in marijuana, Delta(9)-tetrahydrocannabinol

(THC) and cannabidiol (CBD), decrease the production and release of proinflammatory cytokines, including interleukin-1beta, interleukin-6, and interferon (IFN)beta, from LPS-activated microglial cells. The cannabinoid anti-inflammatory action does not seem to involve the CB1 and CB2 cannabinoid receptors or the abn-CBD-sensitive receptors. In addition, we found that THC and CBD act through different, although partially overlapping, mechanisms. CBD, but not THC, reduces the activity of the NF-kappaB pathway, a primary pathway regulating the expression of proinflammatory genes. Moreover, CBD, but not THC, up-regulates the activation of the STAT3 transcription factor, an element of homeostatic mechanism(s) inducing anti-inflammatory events. Following CBD treatment, but less so with THC, we observed a decreased level of mRNA for the Socs3 gene, a main negative regulator of STATs and particularly of STAT3. However, both CBD and THC decreased the activation of the LPS-induced STAT1 transcription factor, a key player in IFNbeta-dependent proinflammatory processes. In summary, our observations show that CBD and THC vary in their effects on the anti-inflammatory pathways, including the NF-kappaB and IFNbeta-dependent pathways.

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Free Radic Biol Med. 2014 Mar;68:260-7. doi: 10.1016/j.freeradbiomed.2013.12.026. Epub 2014 Jan 4.

**Cannabidiol protects liver from binge alcohol-induced steatosis by mechanisms including inhibition of oxidative stress and increase in autophagy.**

Yang L, Rozenfeld R, Wu D, Devi LA, Zhang Z, Cederbaum A.

Abstract

Acute alcohol drinking induces steatosis, and effective prevention of steatosis can protect liver from progressive damage caused by alcohol. Increased oxidative stress has been reported as one mechanism underlying alcohol-induced steatosis. We evaluated whether cannabidiol, which has been reported to function as an antioxidant, can protect the liver from alcohol-generated oxidative stress-induced steatosis. Cannabidiol can prevent acute alcohol-induced liver steatosis in mice, possibly by preventing the increase in oxidative stress and the activation of the JNK MAPK pathway. Cannabidiol per se can increase autophagy both in CYP2E1-expressing HepG2 cells and in mouse liver. Importantly, cannabidiol can prevent the decrease in autophagy induced by alcohol. In conclusion, these results show that cannabidiol protects mouse liver from acute alcohol-induced steatosis through multiple mechanisms including attenuation of alcohol-mediated oxidative stress, prevention of JNK MAPK activation, and increasing autophagy.

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CNS Neurol Disord Drug Targets. 2007 Dec;6(6):377-87.

**Cannabinoids and neuroprotection in motor-related disorders.**

de Lago E, Fernández-Ruiz J.

Abstract

Neuroprotective properties of cannabinoids have been extensively studied in the last years in different neurodegenerative pathologies. This potential is based on the antioxidant, anti-inflammatory and anti-excitotoxic properties exhibited by these compounds that allow them to afford neuroprotection in different neurodegenerative disorders like Parkinson's disease (PD), Huntington's disease (HD), multiple sclerosis (MS) and others. PD and HD are chronic pathologies that are caused by the degeneration of specific structures within the basal ganglia. In both disorders, the key mechanisms involved in the neuroprotection provided by cannabinoids include cannabinoid receptor-independent effects aimed at reducing the oxidative injury, and also cannabinoid 2 receptors (CB2)-mediated effects exerted by regulating the influence of reactive microglia on neuronal homeostasis. MS is an inflammatory demyelinating disorder primarily affecting spinal neurons and secondarily producing a malfunctioning and/or degeneration of other neuronal subpopulations located in supraspinal brain structures. There is evidence that both cannabinoid 1 receptors (CB1) and CB2 may afford a protective effect in this disease due to their immunomodulatory, anti-inflammatory and anti-excitotoxic properties. Lastly, neuroprotective effects of cannabinoids exerted by the activation of CB1 but also CB2 receptors have been also identified in amyotrophic lateral sclerosis (ALS), another degenerative disease characterized by the selective death of spinal motoneurons. In the present review, we will collect the latest advances in the knowledge of the cellular and molecular mechanisms through which cannabinoids might arrest/delay the degeneration of specific neuronal subpopulations in these motor-related disorders. This should serve to encourage that the present promising evidence obtained mainly at the preclinical level might progress to a real exploitation of neuroprotective benefits of potential cannabinoid-based medicines.

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Oncotarget. 2014 Aug; 5(15): 5852–5872.

### **Cannabinoids as therapeutic agents in cancer: current status and future implications**

Bandana Chakravarti, Janani Ravi, and Ramesh K. Ganju

#### **Abstract**

The pharmacological importance of cannabinoids has been in study for several years. Cannabinoids comprise of (a) the active compounds of the *Cannabis sativa* plant, (b) endogenous as well as (c) synthetic cannabinoids. Though cannabinoids are clinically used for anti-palliative effects, recent studies open a promising possibility as anti-cancer agents. They have been shown to possess anti-proliferative and anti-angiogenic effects in vitro as well as in vivo in different cancer models. Cannabinoids regulate key cell signaling pathways that are involved in cell survival, invasion, angiogenesis, metastasis, etc. There is more focus on CB1 and CB2, the two cannabinoid receptors which are activated by most of the cannabinoids. In this review article, we will focus on a broad range of cannabinoids, their receptor dependent and receptor independent functional roles against various cancer types with respect to growth, metastasis, energy metabolism, immune environment, stemness and future perspectives in exploring new possible therapeutic opportunities.

Volume 64, 4 January 2016, Pages 259–266 Progress in Neuro-Psychopharmacology and Biological Psychiatry



## **The use of cannabinoids as anticancer agents**

Guillermo Velasco, Sonia Hernández-Tiedra, David Dávila, Mar Lorente

### **Abstract**

It is well-established that cannabinoids exert palliative effects on some cancer-associated symptoms. In addition, evidences obtained during the last fifteen years support that these compounds can reduce tumor growth in animal models of cancer. Cannabinoids have been shown to activate an ER-stress related pathway that leads to the stimulation of autophagy-mediated cancer cell death. In addition, cannabinoids inhibit tumor angiogenesis and decrease cancer cell migration. The mechanisms of resistance to cannabinoid anticancer action as well as the possible strategies to develop cannabinoid-based combinational therapies to fight cancer have also started to be explored. In this review we will summarize these observations (that have already helped to set the bases for the development of the first clinical studies to investigate the potential clinical benefit of using cannabinoids in anticancer therapies) and will discuss the possible future avenues of research in this area.

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Orv Hetil. 2012 Apr 1;153(13):499-504. doi: 10.1556/OH.2012.29308.

## **The potential use of cannabidiol in the therapy of metabolic syndrome.**

[Article in Hungarian]

Kleiner D, Ditrói K.

### **Abstract**

Cannabidiol, a cannabinoid and serotonin receptor antagonist, may alleviate hyperphagia without the side effects of rimonabant (for example depression and reduced insulin sensitivity). Similar to the peroxisome proliferator-activated receptor-gamma agonists, it may also help the differentiation of adipocytes. Cannabidiol has an immunomodulating effect, as well, that helps lessen the progression of atherosclerosis induced by high glucose level. It may also be effective in fighting ischaemic diseases, the most harmful complications of metabolic syndrome. However, it can only be administered as an adjuvant therapy because of its low binding potency, and its inhibiting effect of cytochrome P450 enzymes should also be considered. Nevertheless, it may be beneficially used in adjuvant therapy because of its few side effects.

Phytother Res. 2013 May;27(5):633-6. doi: 10.1002/ptr.4781. Epub 2012 Jul 20.

## **Cannabidiol in inflammatory bowel diseases: a brief overview.**

Esposito G, Filippis DD, Cirillo C, Iuvone T, Capoccia E, Scuderi C, Steardo A, Cuomo R, Steardo L.

### **Abstract**

This mini review highlights the importance of cannabidiol (CBD) as a promising drug for the therapy of inflammatory bowel diseases (IBD). Actual pharmacological treatments for IBD should be enlarged toward the search for low-toxicity and low-cost drugs that may be given

alone or in combination with the conventional anti-IBD drugs to increase their efficacy in the therapy of relapsing forms of colitis. In the past, Cannabis preparations have been considered new promising pharmacological tools in view of their anti-inflammatory role in IBD as well as other gut disturbances. However, their use in the clinical therapy has been strongly limited by their psychotropic effects. CBD is a very promising compound since it shares the typical cannabinoid beneficial effects on gut lacking any psychotropic effects. For years, its activity has been enigmatic for gastroenterologists and pharmacologists, but now it is evident that this compound may interact at extra-cannabinoid system receptor sites, such as peroxisome proliferator-activated receptor-gamma. This strategic interaction makes CBD as a potential candidate for the development of a new class of anti-IBD drugs.

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Curr Pharm Des. 2012;18(32):5131-40.

**A critical review of the antipsychotic effects of cannabidiol: 30 years of a translational investigation.**

Zuardi AW, Crippa JA, Hallak JE, Bhattacharyya S, Atakan Z, Martin-Santos R, McGuire PK, Guimarães FS.

Abstract

$\Delta(9)$ -tetrahydrocannabinol ( $\Delta(9)$ -THC) is the main compound of the Cannabis Sativa responsible for most of the effects of the plant. Another major constituent is cannabidiol (CBD), formerly regarded to be devoid of pharmacological activity. However, laboratory rodents and human studies have shown that this cannabinoid is able to prevent psychotic-like symptoms induced by high doses of  $\Delta(9)$ -THC. Subsequent studies have demonstrated that CBD has antipsychotic effects as observed using animal models and in healthy volunteers. Thus, this article provides a critical review of the research evaluating antipsychotic potential of this cannabinoid. CBD appears to have pharmacological profile similar to that of atypical antipsychotic drugs as seen using behavioral and neurochemical techniques in animal models. Additionally, CBD prevented human experimental psychosis and was effective in open case reports and clinical trials in patients with schizophrenia with a remarkable safety profile. Moreover, fMRI results strongly suggest that the antipsychotic effects of CBD in relation to the psychotomimetic effects of  $\Delta(9)$ -THC involve the striatum and temporal cortex that have been traditionally associated with psychosis. Although the mechanisms of the antipsychotic properties are still not fully understood, we propose a hypothesis that could have a heuristic value to inspire new studies. These results support the idea that CBD may be a future therapeutic option in psychosis, in general and in schizophrenia, in particular.

Br J Pharmacol. 2012 Nov;167(6):1218-31. doi: 10.1111/j.1476-5381.2012.02050.x.

**Cannabidiol inhibits angiogenesis by multiple mechanisms.**

Solinas M, Massi P, Cantelmo AR, Cattaneo MG, Cammarota R, Bartolini D, Cinquina V, Valenti M, Vicentini LM, Noonan DM, Albini A, Parolaro D.

Abstract

BACKGROUND AND PURPOSE:

Several studies have demonstrated anti-proliferative and pro-apoptotic actions of cannabinoids on various tumours, together with their anti-angiogenic properties. The non-psychoactive cannabinoid cannabidiol (CBD) effectively inhibits the growth of different types of tumours in vitro and in vivo and down-regulates some pro-angiogenic signals produced by glioma cells. As its anti-angiogenic properties have not been thoroughly investigated to date, and given its very favourable pharmacological and toxicological profile, here, we evaluated the ability of CBD to modulate tumour angiogenesis.

#### EXPERIMENTAL APPROACH:

Firstly, we evaluated the effect of CBD on human umbilical vein endothelial cell (HUVEC) proliferation and viability - through [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay and FACS analysis - and in vitro motility - both in a classical Boyden chamber test and in a wound-healing assay. We next investigated CBD effects on different angiogenesis-related proteins released by HUVECs, using an angiogenesis array kit and an ELISA directed at MMP2. Then we evaluated its effects on in vitro angiogenesis in treated HUVECs invading a Matrigel layer and in HUVEC spheroids embedded into collagen gels, and further characterized its effects in vivo using a Matrigel sponge model of angiogenesis in C57/BL6 mice.

#### KEY RESULTS:

CBD induced HUVEC cyto-stasis without inducing apoptosis, inhibited HUVEC migration, invasion and sprouting in vitro, and angiogenesis in vivo in Matrigel sponges. These effects were associated with the down-modulation of several angiogenesis-related molecules.

#### CONCLUSIONS AND IMPLICATIONS:

This study reveals that CBD inhibits angiogenesis by multiple mechanisms. Its dual effect on both tumour and endothelial cells supports the hypothesis that CBD has potential as an effective agent in cancer therapy.

Transl Psychiatry. 2012 Mar 20;2:e94. doi: 10.1038/tp.2012.15.

#### **Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia.**

Leweke FM, Piomelli D, Pahlisch F, Muhl D, Gerth CW, Hoyer C, Klosterkötter J, Hellmich M, Koethe D.

#### Abstract

Cannabidiol is a component of marijuana that does not activate cannabinoid receptors, but moderately inhibits the degradation of the endocannabinoid anandamide. We previously reported that an elevation of anandamide levels in cerebrospinal fluid inversely correlated to psychotic symptoms. Furthermore, enhanced anandamide signaling led to a lower transition rate from initial prodromal states into frank psychosis as well as postponed transition. In our translational approach, we performed a double-blind, randomized clinical trial of cannabidiol vs amisulpride, a potent antipsychotic, in acute schizophrenia to evaluate the clinical relevance of our initial findings. Either treatment was safe and led to significant clinical improvement, but

cannabidiol displayed a markedly superior side-effect profile. Moreover, cannabidiol treatment was accompanied by a significant increase in serum anandamide levels, which was significantly associated with clinical improvement. The results suggest that inhibition of anandamide deactivation may contribute to the antipsychotic effects of cannabidiol potentially representing a completely new mechanism in the treatment of schizophrenia.

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Pharmacol Biochem Behav. 2011 Apr;98(2):268-72. doi: 10.1016/j.pbb.2011.01.007. Epub 2011 Jan 14.

### **Cannabidiol inhibits the hyperphagia induced by cannabinoid-1 or serotonin-1A receptor agonists.**

Scopinho AA, Guimarães FS, Corrêa FM, Resstel LB.

#### **Abstract**

$\Delta$ 9-THC is a component of *Cannabis sativa* that increases food intake in animals and humans, an effect prevented by selective CB1 receptor antagonists. Cannabidiol (CBD) is another constituent of this plant that promotes several opposite neuropharmacological effects compared to  $\Delta$ 9-THC. CBD mechanisms of action are still not clear, but under specific experimental conditions it can antagonize the effects of cannabinoid agonists, block the reuptake of anandamide and act as an agonist of 5-HT<sub>1A</sub> receptors. Since both the cannabinoid and serotonergic systems have been implicated in food intake control, the aim of the present work was to investigate the effects caused by CBD on hyperphagia induced by agonists of CB1 or 5-HT<sub>1A</sub> receptors. Fed or fasted Wistar rats received intraperitoneal (i.p.) injections of CBD (1, 10 and 20 mg/kg) and food intake was measured 30 min later for 1 h. Moreover, additional fed or fasted groups received, after pretreatment with CBD (20 mg/kg) or vehicle, i.p. administration of vehicle, a CB1 receptor agonist WIN55,212-2 (2 mg/kg) or a 5-HT<sub>1A</sub> receptor agonist 8-OH-DPAT (1 mg/kg) and were submitted to the food intake test for 1 h. CBD by itself did not change food intake in fed or fasted rats. However, it prevented the hyperphagic effects induced by WIN55,212-2 or 8-OH-DPAT. These results show that CBD can interfere with food intake changes induced by a CB1 or 5-HT<sub>1A</sub> receptor agonist, suggesting that its role as a possible food intake regulator should be further investigate.

PLoS One. 2011; 6(12): e28668.

### **Cannabidiol Reduces A $\beta$ -Induced Neuroinflammation and Promotes Hippocampal Neurogenesis through PPAR $\gamma$ Involvement**

Giuseppe Esposito, Caterina Scuderi, Marta Valenza, Giuseppina Ines Togna, Valentina Latina, Daniele De Filippis, Mariateresa Cipriano, Maria Rosaria Carratù, Teresa Iuvone, and Luca Steardo

#### **Abstract**

Peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) has been reported to be involved in the etiology of pathological features of Alzheimer's disease (AD). Cannabidiol (CBD), a *Cannabis* derivative devoid of psychomimetic effects, has attracted much attention because of its promising neuroprotective properties in rat AD models, even though the mechanism responsible for such actions remains unknown. This study was aimed at exploring whether CBD effects

could be subordinate to its activity at PPAR $\gamma$ , which has been recently indicated as its putative binding site. CBD actions on  $\beta$ -amyloid-induced neurotoxicity in rat AD models, either in presence or absence of PPAR antagonists were investigated. Results showed that the blockade of PPAR $\gamma$  was able to significantly blunt CBD effects on reactive gliosis and subsequently on neuronal damage. Moreover, due to its interaction at PPAR $\gamma$ , CBD was observed to stimulate hippocampal neurogenesis. All these findings report the inescapable role of this receptor in mediating CBD actions, here reported.

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Neuropsychopharmacology (2010) 35, 764–774; doi:10.1038/npp.2009.184; published online 18 November 2009

### **Opposite Effects of $\Delta$ -9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology**

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$\Delta$ -9-tetrahydrocannabinol ( $\Delta$ -9-THC) and Cannabidiol (CBD), the two main ingredients of the Cannabis sativa plant have distinct symptomatic and behavioral effects. We used functional magnetic resonance imaging (fMRI) in healthy volunteers to examine whether  $\Delta$ -9-THC and CBD had opposite effects on regional brain function. We then assessed whether pretreatment with CBD can prevent the acute psychotic symptoms induced by  $\Delta$ -9-THC. Fifteen healthy men with minimal earlier exposure to cannabis were scanned while performing a verbal memory task, a response inhibition task, a sensory processing task, and when viewing fearful faces. Subjects were scanned on three occasions, each preceded by oral administration of  $\Delta$ -9-THC, CBD, or placebo. BOLD responses were measured using fMRI. In a second experiment, six healthy volunteers were administered  $\Delta$ -9-THC intravenously on two occasions, after placebo or CBD pretreatment to examine whether CBD could block the psychotic symptoms induced by  $\Delta$ -9-THC.  $\Delta$ -9-THC and CBD had opposite effects on activation relative to placebo in the striatum during verbal recall, in the hippocampus during the response inhibition task, in the amygdala when subjects viewed fearful faces, in the superior temporal cortex when subjects listened to speech, and in the occipital cortex during visual processing. In the second experiment, pretreatment with CBD prevented the acute induction of psychotic symptoms by  $\Delta$ -9-tetrahydrocannabinol.  $\Delta$ -9-THC and CBD can have opposite effects on regional brain function, which may underlie their different symptomatic and behavioral effects, and CBD's ability to block the psychotogenic effects of  $\Delta$ -9-THC.