CBD: Inflammation and Oxidative Stress

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[1].

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_1 and CB_2 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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[Indexed for MEDLINE] Free PMC Article

CBD: Pain and inflammation

The Nonpsychotropic Cannabinoid Cannabidiol Modulates and Directly Activates Alpha-1 and Alpha-1-Beta Glycine Receptor Function

Ahrens J.a · Demir R.a · Leuwer M.c · de la Roche J.a · Krampfl K.b · Foadi N.a · Karst M.a · Haeseler G.a
Pharmacology 2009;83:217–222
https://doi.org/10.1159/000201556

Abstract
Loss of inhibitory synaptic transmission within the dorsal horn of the spinal cord plays a key role in the development of chronic pain following inflammation or nerve injury. Inhibitory postsynaptic transmission in the adult spinal cord involves mainly glycine. Cannabidiol is a nonpsychotropic plant constituent of Cannabis sativa. As we hypothesized that non-CB receptor mechanisms of cannabidiol might contribute to its anti-inflammatory and neuroprotective effects, we investigated the interaction of cannabidiol with strychnine-sensitive α1 and α1β glycine receptors by using the whole-cell patch clamp technique. Cannabidiol showed a positive allosteric modulating effect in a low micromolar concentration range (EC50 values: α1 = 12.3 ± 3.8 μmol/l and α1β = 18.1 ± 6.2 μmol/l). Direct activation of glycine receptors was observed at higher concentrations above 100 μmol/l (EC50 values: α1 = 132.4 ± 12.3 μmol/l and α1β = 144.3 ± 22.7 μmol/l). These in vitro results suggest that strychnine-sensitive glycine receptors may be a target for cannabidiol mediating some of its anti-inflammatory and neuroprotective properties.

CBD: modulator of biotransformation (CYP450) enzymes

Drug Metab Pharmacokinet. 2012;27(3):294-300. Epub 2011 Dec 13.

Comparison in the in vitro inhibitory effects of major phytocannabinoids and polycyclic aromatic hydrocarbons contained in marijuana smoke on cytochrome P450 2C9 activity.

Yamaori S1, Koeda K, Kushihara M, Hada Y, Yamamoto I, Watanabe K.
Author information

Abstract

Inhibitory effects of Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol (CBD), and cannabinol (CBN), the three major constituents in marijuana, and polycyclic aromatic hydrocarbons (PAHs) contained in marijuana smoke on catalytic activity of human cytochrome P450 (CYP) 2C9 were investigated. These phytocannabinoids concentration-dependently inhibited S-warfarin 7-hydroxylase and diclofenac 4'-hydroxylase activities of human liver microsomes (HLMs) and recombinant CYP2C9 (rCYP2C9). In contrast, none of the twelve PAHs including benz[a]anthracene and benzo[a]pyrene exerted substantial inhibition (IC_{50} > 10 μM). The inhibitory potentials of Δ^9-THC (Ki = 0.937-1.50 μM) and CBN (Ki = 0.882-1.29 μM) were almost equivalent regardless of the enzyme sources used, whereas the inhibitory potency of CBD (Ki > = 0.954-9.88 μM) varied depending on the enzyme sources and substrates used. Δ^9-THC inhibited both S-warfarin 7-hydroxylase and diclofenac 4'-hydroxylase activities of HLMs and rCYP2C9 in a mixed manner. CBD and CBN competitively inhibited the activities of HLMs and rCYP2C9, with the only notable difference being that CBD and CBN exhibited mixed-type inhibitions against diclofenac 4'-hydroxylation and S-warfarin 7-hydroxylation, respectively, by rCYP2C9. None of Δ^9-THC, CBD, and CBN exerted metabolism-dependent inhibition. These results indicated that the three major phytocannabinoids but not PAHs contained in marijuana smoke potently inhibited CYP2C9 activity and that these cannabinoids can be characterized as direct inhibitors for CYP2C9.

CBD: CYP450 Enzyme modulation

Drug Metab Dispos. 2011 Nov;39(11):2049-56. doi: 10.1124/dmd.111.041384. Epub 2011 Aug 5.

Cannabidiol, a major phytocannabinoid, as a potent atypical inhibitor for CYP2D6.

Yamaori S1, Okamoto Y, Yamamoto I, Watanabe K.
Author information

Abstract
Δ(9)-Tetrahydrocannabinol, cannabidiol (CBD), and cannabinol are the three major cannabinoids contained in marijuana, which are devoid of nitrogen atoms in their structures. In this study, we investigated the inhibitory effects of the major phytocannabinoids on the catalytic activity of human CYP2D6. These major cannabinoids inhibited the 3-[2-(N,N-diethyl-N-methylammonium)ethyl]-7-methoxy-4-methylcoumarin (AMMC) and dextromethorphan O-demethylase activities of recombinant CYP2D6 and pooled human liver microsomes in a concentration-dependent manner (IC(50) = 4.01-24.9 μM), indicating the strongest inhibitory potency of CBD. However, these cannabinoids showed no or weak metabolism-dependent inhibition. CBD competitively inhibited the CYP2D6 activities with the apparent K(i) values of 1.16 to 2.69 μM. To clarify the structural requirement for CBD-mediated CYP2D6 inhibition, effects of CBD-related compounds on the AMMC O-demethylase activity of recombinant CYP2D6 were examined. Olivetol (IC(50) = 7.21 μM) inhibited CYP2D6 activity as potently as CBD did (IC(50) = 6.52 μM), whereas d-limonene did not show any inhibitory effect. Pentylbenzene failed to inhibit CYP2D6 activity. Furthermore, neither monomethyl nor dimethyl ethers of CBD inhibited the activity. Cannabidivarin having a propyl side chain inhibited CYP2D6 activity; its inhibitory effect (IC(50) = 10.2 μM) was less potent than that of CBD. On the other hand, orcinol and resorcinol showed lack of inhibition. The inhibitory effect of CBD on CYP2D6 activity was more potent than those of 16 compounds without nitrogen atoms tested, such as progesterone. These results indicated that CBD caused potent direct CYP2D6 inhibition, in which two phenolic hydroxyl groups and the pentyl side chain of CBD may play important roles.

PMID:
21821735
DOI:
10.1124/dmd.111.041384

CBD: Modulates CYP450 Enzymes

Drug Metab Pharmacokinet. 2013;28(4):332-8. Epub 2013 Jan 15.

Cannabidiol is a potent inhibitor of the catalytic activity of cytochrome P450 2C19.

Jiang R1, Yamaori S, Okamoto Y, Yamamoto I, Watanabe K.
Author information

Abstract
The present study investigated the inhibitory effect of cannabidiol (CBD), a major constituent of marijuana, on the catalytic activity of cytochrome P450 2C19 (CYP2C19). (S)-Mephenytoin 4'-hydroxylase activities of human liver microsomes (HLMs) and recombinant CYP2C19 were inhibited by CBD in a concentration-dependent manner (IC_{50} = 8.70 and 2.51 μM, respectively). Omeprazole 5-hydroxylase and 3-O-methylfluorescein O-demethylase activities in recombinant CYP2C19 were also strongly inhibited by CBD (IC_{50} = 1.55 and 1.79 μM, respectively). Kinetic analysis for inhibition revealed that CBD showed a mixed-type inhibition against (S)-mephenytoin 4'-hydroxylation by recombinant CYP2C19. To clarify the structural requirements for CBD-mediated CYP2C19 inhibition, the effects of CBD-related compounds on CYP2C19 activity were examined. Olivetol inhibited the (S)-mephenytoin 4'-hydroxylase activity of recombinant CYP2C19 with the IC_{50} value of 15.3 μM, whereas d-limonene slightly inhibited the activity (IC_{50} > 50 μM). The inhibitory effect of CBD-2'-monomethyl ether (IC_{50} = 1.88 μM) on CYP2C19 was comparable to that of CBD, although the inhibitory potency of CBD-2',6'-dimethyl ether (IC_{50} = 14.8 μM) was lower than that of CBD. Cannabidivarin, possessing a propyl side chain, showed slightly less potent inhibition (IC_{50} = 3.45 μM) as compared with CBD, whereas orcinol and resorcinol did not inhibit CYP2C19 activity at all. These results indicate that CBD caused potent CYP2C19 inhibition, in which one free phenolic hydroxyl group and the pentyl side chain of CBD may play important roles.

CYMENE: found in PoP Hemp extract: antioxidant

Inflammation. 2014 Apr;37(2):358-64. doi: 10.1007/s10753-013-9747-3.

Protective effect of p-cymene on lipopolysaccharide-induced acute lung injury in mice.

Chen L1, Zhao L, Zhang C, Lan Z.
Author information

Abstract
In the previous study, the anti-inflammatory effect of p-cymene had been found. In this study, we investigated anti-inflammatory effects of p-cymene on acute lung injury using lipopolysaccharide (LPS)-induced acute lung injury (ALI) mouse model. The cell counting in the bronchoalveolar lavage fluid (BALF) was measured. The animal lung edema degree was evaluated by wet/dry weight (W/D) ratio. The superoxidase dismutase (SOD) activity and myeloperoxidase (MPO) activity was assayed by SOD and MPO kits, respectively. The levels of inflammatory mediators including tumor necrosis factor alpha (TNF-α), IL-1β, and IL-6 were assayed by enzyme-linked immunosorbent assay method. The pathological changes of the lung tissues were observed by hematoxylin and eosin staining. The inflammatory signal pathway-related protein levels of NF-κB were measured using Western blotting. The data showed that treatment with the p-cymene markedly attenuated inflammatory cell numbers in the BALF, decreased NF-κB protein level in the lungs, improved SOD activity, and inhibited MPO activity. Histological studies demonstrated that p-cymene substantially inhibited LPS-induced neutrophils in the lung tissue compared with the model group. The results indicated that p-cymene had a protective effect on LPS-induced ALI in mice.

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24085645
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10.1007/s10753-013-9747-3
[Indexed for MEDLINE]

CYMENE: antioxidant

Pharm Biol. 2015 Mar;53(3):423-8. doi: 10.3109/13880209.2014.923003. Epub 2014 Dec 4.

Evaluation of p-cymene, a natural antioxidant.

de Oliveira TM1, de Carvalho RB, da Costa IH, de Oliveira GA, de Souza AA, de Lima SG, de Freitas RM.
Author information

Abstract
CONTEXT:
Several studies have demonstrated that essential oils and their major components have antioxidant activity. p-Cymene is a monoterpene and a major constituent of essential oils of various species of plants.
OBJECTIVE:
This paper evaluated the antioxidant potential of p-cymene in the hippocampus of mice by determining the levels of thiobarbituric acid reactive substances (TBARS), nitrite content, and activity of catalase (CAT) and superoxide dismutase (SOD).
MATERIALS AND METHODS:
Swiss mice were intraperitoneally treated with 0.05% Tween 80 dissolved in 0.9% saline solution, ascorbic acid 250 mg/kg, and p-cymene at doses of 50, 100, and 150 mg/kg, respectively. After treatment, all groups were observed for 24 h, afterwards, the groups were euthanized for removal of the brain and dissection of the hippocampus.
RESULTS:
The results of treatment with p-cymene were a significant decrease in lipid peroxidation and nitrite content at a dose of CYM 50: 65.54%, CYM 100: 73.29%, CYM 150: 89.83%, and CYM 50: 71.21%; CYM 100: 68.61% and CYM 150:67%, respectively, when compared with the control group. The results showed that at all tested doses, p-cymene produces an increase in SOD and catalase activity significantly at a dose of CYM 50: 22.7%, CYM 100: 33.9%, CYM 150: 63.1%, and CYM 50: 119.25%, CYM 100: 151.83% and CYM 150: 182.70%, respectively, when compared with the vehicle-treated group.
DISCUSSION AND CONCLUSION:
The result of this study shows that p-cymene has an antioxidant potential in vivo and may act as a neuroprotective agent in the brain. This compound may present a new strategy in the development of treatment for many diseases in which oxidative stress plays an important pathophysiological role.

KEYWORDS:
Catalase; lipid peroxidation; monoterpene; nitrite; superoxide dismutase

Cymene: pain relief

ISRN Toxicol. 2013 Jan 14;2013:459530. doi: 10.1155/2013/459530. Print 2013.

Antinociceptive Activity and Redox Profile of the Monoterpenes (+)-Camphene, p-Cymene, and Geranyl Acetate in Experimental Models.

Quintans-Júnior L1, Moreira JC, Pasquali MA, Rabie SM, Pires AS, Schröder R, Rabelo TK, Santos JP, Lima PS, Cavalcanti SC, Araújo AA, Quintans JS, Gelain DP.
Author information

Abstract
OBJECTIVE:
To evaluate antinocicpetive and redox properties of the monoterpenes (+)-camphene, p-cymene, and geranyl acetate in in vivo and in vitro experimental models.
METHODS:
Evaluation of the in vitro antioxidant activity of (+)-camphene, p-cymene, and geranyl acetate using different free radical-generating systems and evaluation of antinociceptive actions by acetic acid-induced writhing and formalin-induced nociception tests in mice.
RESULTS:
p-Cymene has the strongest antinociceptive effect, but (+)-camphene and geranyl acetate also present significant activity at high doses (200 mg/kg). (+)-Camphene had the strongest antioxidant effect in vitro at TBARS and TRAP/TAR assays and also had the highest scavenging activities against different free radicals, such as hydroxyl and superoxide radicals. Sodium nitroprussiate-derived NO production was enhanced by (+)-camphene. Geranyl acetate and p-cymene also presented some antioxidant effects, but with a varying profile according the free radical-generating system studied.
CONCLUSION:
(+)-Camphene, p-cymene, and geranyl acetate may present pharmacological properties related to inflammation and pain-related processes, being potentially useful for development of new therapeutic strategies, with limited possibilities for p-cymene and geranyl acetate.

PMID:
23724298
PMCID:
PMC3658412

Caryophyllene: Abundant terepene in PoP tablets: Antiinflammatory, anti-allergy

Antiinflamm Antiallergy Agents Med Chem. 2014 Mar;13(1):45-55.

Beta caryophyllene and caryophyllene oxide, isolated from Aegle marmelos, as the potent anti-inflammatory agents against lymphoma and neuroblastoma cells.

Sain S, Naoghare PK, Devi SS, Daiwile A, Krishnamurthi K, Arrigo P, Chakrabarti T1.
Author information

Abstract
Aegle marmelos (Indian Bael) is a tree which belongs to the family of Rutaceae. It holds a prominent position in both Indian medicine and Indian culture. We have screened various fractions of Aegle marmelos extracts for their anticancer properties using in vitro cell models. Gas chromatography-Mass spectrometry (GC-MS) was employed to analyze the biomolecules present in the Aegle marmelos extract. Jurkat and human neuroblastoma (IMR-32) cells were treated with different concentrations of the fractionated Aegle marmelos extracts. Flow cytometric analysis revealed that optimal concentration (50 µg/ml) of beta caryophyllene and caryophyllene oxide fractions of Aegle marmelos extract can induce apoptosis in Jurkat cell line. cDNA expression profiling of pro-apoptotic and anti-apoptotic genes was carried out using real time PCR (RT-PCR). Down-regulation of anti-apoptotic genes (bcl-2, mdm2, cox2 and cmyb) and up-regulation of pro-apoptotic genes (bax, bak1, caspase-8, caspase-9 and ATM) in Jurkat and IMR-32 cells treated with the beta caryophyllene and caryophyllene oxide fractions of Aegle marmelos extract revealed the insights of the downstream apoptotic mechanism. Furthermore, in-silico approach was employed to understand the upstream target involved in the induction of apoptosis by the beta caryophyllene and caryophyllene oxide fractions of Aegle marmelos extract. Herein, we report that beta caryophyllene and caryophyllene oxide isolated from Aegle marmelos can act as potent anti-inflammatory agents and modulators of a newly established therapeutic target, 15-lipoxygenase (15-LOX). Beta caryophyllene and caryophyllene oxide can induce apoptosis in lymphoma and neuroblastoma cells via modulation of 15-LOX (up-stream target) followed by the down-regulation of anti-apoptotic and up-regulation of pro-apoptotic genes.

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24484210

[Indexed for MEDLINE]

CBD: better than “Imitrex” for migraines? Serotonin modulator.

Int J Clin Pharmacol Res. 1985;5(4):243-6.

Cannabinoids block release of serotonin from platelets induced by plasma from migraine patients.

Volfe Z, Dvilansky A, Nathan I.

Abstract
The effects were assessed of delta'THC (the psychoactive component of cannabis) and CBD and DMHP-CBD (the non-psychomimetic components of marijuana derivatives) on 14C labelled serotonin release from normal platelets, when incubated with patient's plasma obtained during migraine attack. A statistically significant inhibitory effect (p greater than 0.005) of 14C serotonin release was found at 10(-5)M, 10(-6)M, 10(-7)M delta'THC concentrations. Plasma of migraine patients obtained in attack-free periods revealed no significant inhibitory effect on 14C serotonin release from normal platelets using the same delta'THC concentration. CBD and DMHP-CBD had no significant inhibitory effect on 14C serotonin release from normal platelets when tested either at migraine-free period plasma or plasma obtained during migraine attack.

PMID:
2997048
[Indexed for MEDLINE]

Cannabidiol (CBD) and its analogs: a review of their effects on inflammation.

Burstein S.

Bioorg Med Chem. 2015 Apr 1;23(7):1377-85. doi: 10.1016/j.bmc.2015.01.059. Epub 2015 Feb 7. Review.
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25703248
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Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis.

De Filippis D, Esposito G, Cirillo C, Cipriano M, De Winter BY, Scuderi C, Sarnelli G, Cuomo R, Steardo L, De Man JG, Iuvone T.

PLoS One. 2011;6(12):e28159. doi: 10.1371/journal.pone.0028159. Epub 2011 Dec 6.
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Cannabidiol improves lung function and inflammation in mice submitted to LPS-induced acute lung injury.

Ribeiro A, Almeida VI, Costola-de-Souza C, Ferraz-de-Paula V, Pinheiro ML, Vitoretti LB, Gimenes-Junior JA, Akamine AT, Crippa JA, Tavares-de-Lima W, Palermo-Neto J.

Immunopharmacol Immunotoxicol. 2015 Feb;37(1):35-41. doi: 10.3109/08923973.2014.976794. Epub 2014 Oct 30.
PMID:
25356537
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Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors.

Mecha M, Feliú A, Iñigo PM, Mestre L, Carrillo-Salinas FJ, Guaza C.

Neurobiol Dis. 2013 Nov;59:141-50. doi: 10.1016/j.nbd.2013.06.016. Epub 2013 Jul 11.
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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.
Phytother Res. 2013 May;27(5):633-6. doi: 10.1002/ptr.4781. Epub 2012 Jul 20. Review.
PMID:
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Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress.

Booz GW.
Free Radic Biol Med. 2011 Sep 1;51(5):1054-61. doi: 10.1016/j.freeradbiomed.2011.01.007. Epub 2011 Jan 14. Review.
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Evaluation of the role of the cannabidiol system in an animal model of ischemia/reperfusion kidney injury.

Soares RZ, Vuolo F, Dall'Igna DM, Michels M, Crippa JA, Hallak JE, Zuardi AW, Dal-Pizzol F.
Rev Bras Ter Intensiva. 2015 Oct-Dec;27(4):383-9. doi: 10.5935/0103-507X.20150064. English, Portuguese.
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Cannabidiol (CBD) enhances lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice.

Karmaus PW, Wagner JG, Harkema JR, Kaminski NE, Kaplan BL.
J Immunotoxicol. 2013 Jul-Sep;10(3):321-8. doi: 10.3109/1547691X.2012.741628. Epub 2012 Nov 23.
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Cannabidiol protects oligodendrocyte progenitor cells from

inflammation-induced apoptosis by attenuating endoplasmic reticulum stress.

Mecha M, Torrao AS, Mestre L, Carrillo-Salinas FJ, Mechoulam R, Guaza C.
Cell Death Dis. 2012 Jun 28;3:e331. doi: 10.1038/cddis.2012.71.
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Cannabidiol rescues acute hepatic toxicity and seizure induced by cocaine.

Vilela LR, Gomides LF, David BA, Antunes MM, Diniz AB, Moreira Fde A, Menezes GB.
Mediators Inflamm. 2015;2015:523418. doi: 10.1155/2015/523418. Epub 2015 Apr 27.
PMID:
25999668
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Experimental cannabidiol treatment reduces early pancreatic inflammation in type 1 diabetes.

Lehmann C, Fisher NB, Tugwell B, Szczesniak A, Kelly M, Zhou J.
Clin Hemorheol Microcirc. 2016;64(4):655-662. doi: 10.3233/CH-168021.
PMID:
27767974
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Protective effects of cannabidiol on lesion-induced intervertebral disc degeneration.

Silveira JW, Issy AC, Castania VA, Salmon CE, Nogueira-Barbosa MH, Guimarães FS, Defino HL, Del Bel E.
PLoS One. 2014 Dec 17;9(12):e113161. doi: 10.1371/journal.pone.0113161. eCollection 2014.
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Cannabinoid actions at TRPV channels: effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation.

De Petrocellis L, Orlando P, Moriello AS, Aviello G, Stott C, Izzo AA, Di Marzo V.
Acta Physiol (Oxf). 2012 Feb;204(2):255-66. doi: 10.1111/j.1748-1716.2011.02338.x. Epub 2011 Aug 12.
PMID:
21726418
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Cannabidiol reduces lipopolysaccharide-induced vascular changes and inflammation in the mouse brain: an intravital microscopy study.

Ruiz-Valdepeñas L, Martínez-Orgado JA, Benito C, Millán A, Tolón RM, Romero J.
J Neuroinflammation. 2011 Jan 18;8(1):5. doi: 10.1186/1742-2094-8-5.
PMID:
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Cannabidiol, a non-psychotropic plant-derived cannabinoid, decreases inflammation in a murine model of acute lung injury: role for the adenosine A(2A) receptor.

Ribeiro A, Ferraz-de-Paula V, Pinheiro ML, Vitoretti LB, Mariano-Souza DP, Quinteiro-Filho WM, Akamine AT, Almeida VI, Quevedo J, Dal-Pizzol F, Hallak JE, Zuardi AW, Crippa JA, Palermo-Neto J.
Eur J Pharmacol. 2012 Mar 5;678(1-3):78-85. doi: 10.1016/j.ejphar.2011.12.043. Epub 2012 Jan 12.
PMID:
22265864
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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.
Daru. 2015 Oct 21;23:48. doi: 10.1186/s40199-015-0131-8.
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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.
Eur J Pain. 2016 Jul;20(6):936-48. doi: 10.1002/ejp.818. Epub 2015 Oct 30.
PMID:
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Long-term cannabidiol treatment prevents the development of social recognition memory deficits in Alzheimer's disease transgenic mice.

Cheng D, Spiro AS, Jenner AM, Garner B, Karl T.
J Alzheimers Dis. 2014;42(4):1383-96. doi: 10.3233/JAD-140921.
PMID:
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Flax Fiber Hydrophobic Extract Inhibits Human Skin Cells Inflammation and Causes Remodeling of Extracellular Matrix and Wound Closure Activation.

Styrczewska M, Kostyn A, Kulma A, Majkowska-Skrobek G, Augustyniak D, Prescha A, Czuj T, Szopa J.
Biomed Res Int. 2015;2015:862391. doi: 10.1155/2015/862391. Epub 2015 Aug 4.
PMID:
26347154
Free PMC Article
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Protective effect of cannabidiol on hydrogen peroxide−induced apoptosis, inflammation and oxidative stress in nucleus pulposus cells.

Chen J, Hou C, Chen X, Wang D, Yang P, He X, Zhou J, Li H.
Mol Med Rep. 2016 Sep;14(3):2321-7. doi: 10.3892/mmr.2016.5513. Epub 2016 Jul 13.
PMID:
27430346
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CBD: Peripheral neuropathy

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 SJ1, 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 $mg \cdot kg^{-1}$) in female C57Bl/6 mice. This effect was reversed by co-administration of the 5-HT(1A) antagonist WAY 100635, but not the CB_1 antagonist SR141716 or the CB_2 antagonist SR144528. CBD produced no conditioned rewarding effects and did not affect conditioned learning and memory. Also, CBD + PAC combinations produce additive to synergistic inhibition of breast cancer cell viability.
CONCLUSIONS AND IMPLICATIONS:
Our data suggest that CBD is protective against PAC-induced neurotoxicity mediated in part by the 5-HT(1A) receptor system. Furthermore, CBD treatment was devoid of conditioned rewarding effects or cognitive impairment and did not attenuate PAC-induced inhibition of breast cancer cell viability. Hence, adjunct treatment with CBD during PAC chemotherapy may be safe

and effective in the prevention or attenuation of CIPN.

KEYWORDS:
5-HT1A; CIPN; breast cancer; cannabidiol; cannabinoid; chemotherapy-induced neuropathic pain; mechanical sensitivity; paclitaxel
PMID:
24117398
PMCID:
PMC3969077
DOI:
10.1111/bph.12439
[Indexed for MEDLINE]
Free PMC Article

CBD: Peripheral Neuropathy (Chemo-induced)

J Pain Symptom Manage. 2014 Jan;47(1):166-73. doi: 10.1016/j.jpainsymman.2013.02.018. Epub 2013 Jun 4.

A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain.

Lynch ME1, Cesar-Rittenberg P2, Hohmann AG3.
Author information

Abstract
CONTEXT:
Neuropathic pain caused by chemotherapy limits dosing and duration of potentially life-saving anti-cancer treatment and impairs quality of life. Chemotherapeutic neuropathy responds poorly to conventional treatments, and there is an urgent medical need for new treatments. Recent preclinical studies demonstrate that cannabinoid agonists suppress established chemotherapy-evoked neuropathy.
OBJECTIVES:
This was a pilot trial to begin to investigate a currently available cannabinoid agent, nabiximols (oral mucosal spray containing cannabinoids), in the treatment of chemotherapy-induced neuropathic pain.
METHODS:
A randomized, placebo-controlled crossover pilot study was done in 16 patients with established chemotherapy-induced neuropathic pain. A 0-10 point numeric rating scale for pain intensity (NRS-PI) was used as the primary outcome measure.
RESULTS:
When examining the whole group, there was no statistically significant difference between the treatment and the placebo groups on the NRS-PI. A responder analysis demonstrated that there were five participants who reported a two-point or greater reduction in pain that trended toward statistical significance and the number needed to treat was five.
CONCLUSION:
Chemotherapy-induced neuropathic pain is particularly resistant to currently available treatments. This pilot trial found a number needed to treat of five and an average decrease of 2.6 on an 11-point NRS-PI in five "responders" (as compared with a decrease of 0.6 with placebo) and supports that it is worthwhile to study nabiximols in a full randomized, placebo-

controlled trial of chemotherapy-induced neuropathic pain.

KEYWORDS:
Neuropathic pain; cannabinoids; chemotherapy; randomized controlled trial
PMID:
23742737
DOI:
10.1016/j.jpainsymman.2013.02.018

CBD: nerve pain

J Neurol. 2015 Jan;262(1):27-40. doi: 10.1007/s00415-014-7502-9. Epub 2014 Sep 30.

A multicentre, open-label, follow-on study to assess the long-term maintenance of effect, tolerance and safety of THC/CBD oromucosal spray in the management of neuropathic pain.

Hoggart B1, Ratcliffe S, Ehler E, Simpson KH, Hovorka J, Lejčko J, Taylor L, Lauder H, Serpell M.

Author information

Abstract

Peripheral neuropathic pain (PNP) poses a significant clinical challenge. The long-term efficacy of delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray was investigated in this 38-week open-label extension study. In total, 380 patients with PNP associated with diabetes or allodynia entered this study from two parent randomised, controlled trials. Patients received THC/CBD spray for a further 38 weeks in addition to their current analgesic therapy. Neuropathic pain severity was the primary efficacy measure using a pain 0-10 numerical rating scale (NRS). Additional efficacy, safety and tolerability outcomes were also investigated. In total, 234 patients completed the study (62 %). The pain NRS showed a decrease in score over time in patients from a mean of 6.9 points (baseline in the parent studies) to a mean of 4.2 points (end of open-label follow-up). The proportion of patients who reported at least a clinically relevant 30 % improvement in pain continued to increase with time (up to 9 months); at least half of all patients reported a 30 % improvement at all time points. Improvements were observed for all secondary efficacy outcomes, including sleep quality 0-10 NRS scores, neuropathic pain scale scores, subject global impression of change and EQ-5D questionnaire scores. THC/CBD spray was well tolerated for the study duration and patients did not seek to increase their dose with time, with no new safety concerns arising from long-term use. In this previously difficult to manage patient population, THC/CBD spray was beneficial for the majority of patients with PNP associated with diabetes or allodynia.

PMID:
25270679
DOI:
10.1007/s00415-014-7502-9

CBD: Opiate receptors (pain and addiction)

J Neurol Sci. 2014 Dec 15;347(1-2):82-9. doi: 10.1016/j.jns.2014.09.024. Epub 2014 Sep 23.

Cannabidiol and endogenous opioid peptide-mediated mechanisms modulate antinociception induced by transcutaneous electrostimulation of the peripheral nervous system.

Gonçalves TC1, Londe AK1, Albano RI2, de Araújo Júnior AT3, de Aguiar Azeredo M2, Biagioni AF2, Vasconcellos TH4, Dos Reis Ferreira CM5, Teixeira DG6, de Souza Crippa JA7, Vieira D8, Coimbra NC9.
Author information

Abstract
Transcutaneous electrical nerve stimulation (TENS) is a non-pharmacological therapy for the treatment of pain. The present work investigated the effect of cannabidiol, naloxone and diazepam in combination with 10 Hz and 150 Hz TENS. Male Wistar rats were submitted to the tail-flick test (baseline), and each rodent received an acute administration (intraperitoneal) of naloxone (3.0mg/kg), diazepam (1.5mg/kg) or cannabidiol (0.75 mg/kg, 1.5mg/kg, 3.0mg/kg, 4.5mg/kg, 6.0mg/kg and 12.0mg/kg); 10 min after the acute administration, 10 Hz or 150 Hz TENS or a sham procedure was performed for 30 min. Subsequently, tail-flick measures were recorded over a 90-min period, at 5-min intervals. 10 Hz TENS increased the nociceptive threshold during the 90-min period. This antinociceptive effect was reversed by naloxone pre-treatment, was not altered by diazepam pre-treatment and was abolished by cannabidiol pre-treatment (1.5mg/kg). Moreover, 150 Hz TENS increased tail-flick latencies by 35 min post-treatment, which was partially inhibited by naloxone pre-treatment and totally inhibited by cannabidiol (1.5mg/kg). These data suggest the involvement of the endogenous opioid system and the cannabinoid-mediated neuromodulation of the antinociception induced by transcutaneous electrostimulation at 10 Hz and 150 Hz TENS.

KEYWORDS:
Cannabidiol; Endogenous opioid peptides; GABA(A) receptor; Pain; Peripheral nervous system; Transcutaneous electrical stimulation

CBD: inflammation

AAPS J. 2009 Mar;11(1):109-19. doi: 10.1208/s12248-009-9084-5. Epub 2009 Feb 6.

Cannabinoids, endocannabinoids, and related analogs in inflammation.

Burstein SH1, Zurier RB.
Author information

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.

PMID:
19199042
PMCID:
PMC2664885
DOI:
10.1208/s12248-009-9084-5
[Indexed for MEDLINE]
Free PMC Article

CBD: Painful Inflammatory conditions: Endocannabinoid deficiency?

Neuro Endocrinol Lett. 2004 Feb-Apr; 25(1-2):31-9.

Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

Russo EB1.
Author information
Abstract
OBJECTIVES:
This study examines the concept of clinical endocannabinoid deficiency (CECD), and the prospect that it could underlie the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome, and other functional conditions alleviated by clinical cannabis.
METHODS:
Available literature was reviewed, and literature searches pursued via the National Library of Medicine database and other resources.
RESULTS:
Migraine has numerous relationships to endocannabinoid function. Anandamide (AEA) potentiates 5-HT1A and inhibits 5-HT2A receptors supporting therapeutic efficacy in acute and preventive migraine treatment. Cannabinoids also demonstrate dopamine-blocking and anti-inflammatory effects. AEA is tonically active in the periaqueductal gray matter, a migraine generator. THC modulates glutamatergic neurotransmission via NMDA receptors. Fibromyalgia is now conceived as a central sensitization state with secondary hyperalgesia. Cannabinoids have similarly demonstrated the ability to block spinal, peripheral and gastrointestinal mechanisms that promote pain in headache, fibromyalgia, IBS and related disorders. The past and potential clinical utility of cannabis-based medicines in their treatment is discussed, as are

further suggestions for experimental investigation of CECD via CSF examination and neuro-imaging.
CONCLUSION:
Migraine, fibromyalgia, IBS and related conditions display common clinical, biochemical and pathophysiological patterns that suggest an underlying clinical endocannabinoid deficiency that may be suitably treated with cannabinoid medicines.
Republished in
Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? [Neuro Endocrinol Lett. 2008]
PMID:
15159679
[Indexed for MEDLINE]

CBD: Modulates anadamide in migraine

J Headache Pain. 2011 Apr;12(2):177-83. doi: 10.1007/s10194-010-0274-4. Epub 2011 Feb 18.

Effects of anandamide in migraine: data from an animal model.

Greco R1, Mangione AS, Sandrini G, Maccarrone M, Nappi G, Tassorelli C.
Author information

Abstract
Systemic nitroglycerin (NTG) produces spontaneous-like migraine attacks in migraine sufferers and induces a condition of hyperalgesia in the rat 4 h after its administration. Endocannabinoid system seems to be involved in the modulation of NTG-induced hyperalgesia, and probably, in the pathophysiological mechanisms of migraine. In this study, the analgesic effect of anandamide (AEA) was evaluated by means of the formalin test, performed in baseline conditions and following NTG-induced hyperalgesia in male Sprague-Dawley rats. AEA was administered 30 min before the formalin injection. In addition, the effect of AEA (administered 30 min before NTG injection) was investigated on NTG-induced Fos expression and evaluated 4 h following NTG injection. AEA induced a significant decrease in the nociceptive behavior during both phases of the formalin test in the animals treated with vehicle, while it abolished NTG-induced hyperalgesia during the phase II. Pre-treatment with AEA significantly reduced the NTG-induced neuronal activation in nucleus trigeminalis caudalis, confirming the results obtained in our previous study, and in area postrema, while the same treatment induced an increase of Fos expression in paraventricular and supraoptic nuclei of the hypothalamus, parabrachial nucleus, and periaqueductal grey. The study confirms that a dysfunction of the endocannabinoid system may contribute to the development of migraine attacks and that a pharmacological modulation of CB receptors can be useful for the treatment of migraine pain.

PMID:
21331757
PMCID:
PMC3072518
DOI:
10.1007/s10194-010-0274-4
[Indexed for MEDLINE]
Free PMC Article

CBD: Post traumatic pain

Concussion. 2017 Oct 4;2(4):CNC49. doi: 10.2217/cnc-2017-0010. eCollection 2017 Dec.

Understanding the endocannabinoid system as a modulator of the trigeminal pain response to concussion.

Elliott MB1,1, Ward SJ2,2, Abood ME3,3, Tuma RF4,4, Jallo JI1,1.
Author information

Abstract
Post-traumatic headache is the most common symptom of postconcussion syndrome and becomes a chronic neurological disorder in a substantial proportion of patients. This review provides a brief overview of the epidemiology of postconcussion headache, research models used to study this disorder, as well as the proposed mechanisms. An objective of this review is to enhance the understanding of how the endogenous cannabinoid system is essential for maintaining the balance of the CNS and regulating inflammation after injury, and in turn making the endocannabinoid system a potential modulator of the trigeminal response to concussion. The review describes the role of endocannabinoid modulation of pain and the potential for use of phytocannabinoids to treat pain, migraine and concussion.

KEYWORDS:
cannabinoid; concussion trigeminal; endocannabinoid; migraine; post-traumatic headache
PMID:
30202590
PMCID:
PMC6122691
DOI:
10.2217/cnc-2017-0010
Free PMC Article

CBD: Migraine

Cephalalgia. 2006 Mar;26(3):277-81.

Biochemical changes in endocannabinoid system are expressed in platelets of female but not male migraineurs.

Cupini LM1, Bari M, Battista N, Argirò G, Finazzi-Agrò A, Calabresi P, Maccarrone M.
Author information

Abstract
The endogenous cannabinoid anandamide (AEA) plays important roles in modulating pain. Head pain is an almost universal human experience, yet primary headache disorders, such as migraine without aura (MoA) or episodic tension-type headache (ETTH), can represent a serious threat to well-being when frequent and disabling. We assessed the discriminating role of endocannabinoids among patients with ETTH or MoA, and control subjects. We measured the activity of AEA hydrolase and AEA transporter, and the level of cannabinoid receptors in peripheral platelets from MoA, ETTH and healthy controls. Sixty-nine headache patients and 36 controls were selected. Diagnosis of headache type was made according to the International Headache Society criteria. We observed significant sex differences concerning AEA membrane transporter and fatty acid amide hydrolase activity in all groups. An increase in the activity of AEA hydrolase and AEA transporter was found in female but not male migraineurs. Cannabinoid receptors were the same in all groups. Here we show that the endocannabinoid system in human platelets is altered in female but not male migraneurs. Our results suggest that in migraineur women an increased AEA degradation by platelets, and hence a reduced concentration of AEA in blood, might reduce the pain threshold and possibly explain the prevalence of migraine in women. The involvement of the endocannabinoid system in migraine is new and broadens our knowledge of this widespread and multifactorial disease.

PMID:
16472333
DOI:
10.1111/j.1468-2982.2005.01031.x
[Indexed for MEDLINE]

CBD: headaches

Eur J Clin Pharmacol. 2008 Jan;64(1):1-8. Epub 2007 Nov 15.

Endocannabinoids in platelets of chronic migraine patients and medication-overuse headache patients: relation with serotonin levels.

Rossi C1, Pini LA, Cupini ML, Calabresi P, Sarchielli P.
Author information

Abstract
BACKGROUND:
Chronic migraine (CM) and medication-overuse headaches (MOH) are well-recognized disabling conditions affecting a significant portion of the headache population attending centers specialized in treating headaches. A dysfunctioning of the serotonergic system has been demonstrated in MOH and CM patients. Here we report on our assessment of the dysfunctioning of the endocannabinoid system as a potential underlying factor in pathogenic mechanisms involved in CM and MOH.
METHOD:
To test the hypothesis of an impairment in the endocannabinoid system in patients with MOH and CM and to assess its relationship with any disruption of the serotonergic system, we determined the levels of the two main endogenous cannabinoids, anandamide (AEA) and 2-acylglycerol (2-AG), in platelets of 20 CM patients, 20 MOH patients and 20 control subjects and also measured the platelet serotonin levels in the same patients.
RESULTS:
We found that 2-AG and AEA levels were significantly lower in MOH patients and CM patients than in the control subjects, without significant differences between the two patient groups. Serotonin levels were also strongly reduced in the two patient groups and were correlated with 2-AG levels, with higher values for MOH patients.
CONCLUSION:
These data support the potential involvement of a dysfunctioning of the endocannabinoid and serotonergic systems in the pathology of CM and MOH. These systems appear to be mutually related and able to contribute to the chronification of both CM and MOH.

PMID:
18004553
DOI:
10.1007/s00228-007-0391-4
[Indexed for MEDLINE]

Neurobiol Dis. 2008 May;30(2):186-9. doi: 10.1016/j.nbd.2008.01.003. Epub 2008 Feb 1.
Degradation of endocannabinoids in chronic migraine and medication overuse headache.
Cupini LM1, Costa C, Sarchielli P, Bari M, Battista N, Eusebi P, Calabresi P, Maccarrone M.

Author information

Abstract

Chronic migraine (CM) is frequently associated with medication overuse headache (MOH). The endocannabinoid system plays a role in modulating pain including headache and is involved in the common neurobiological mechanism underlying drug addiction and reward system. Anandamide (AEA) and 2-arachidonoylglycerol are the most biologically active endocannabinoids, which bind to both central and peripheral cannabinoid receptors. The level of AEA in the extracellular space is controlled by cellular uptake via a specific AEA membrane transporter (AMT), followed by intracellular degradation by the enzyme AEA hydrolase (fatty acid amide hydrolase, FAAH). AMT and FAAH have also been characterized in human platelets. We assayed the activity of AMT and of FAAH in platelets isolated from four groups of subjects: MOH, CM without MOH, episodic migraine and controls. AMT and FAAH were significantly reduced in CM and MOH, compared to either controls or episodic migraine group. This latter finding was observed in both males and females with CM and MOH. Changes observed in the biochemical mechanisms degrading endogenous cannabinoids may reflect an adaptative behaviour induced by chronic headache and/or drug overuse.

PMID:
18358734
DOI:
10.1016/j.nbd.2008.01.003
[Indexed for MEDLINE]

Behav Pharmacol. 2015 Apr;26(3):304-14. doi: 10.1097/FBP.0000000000000119.
Distinct interactions of cannabidiol and morphine in three nociceptive behavioral models in mice.
Neelakantan H1, Tallarida RJ, Reichenbach ZW, Tuma RF, Ward SJ, Walker EA.
Author information
Abstract
Cannabinoid and opioid agonists can display overlapping behavioral effects and the combination of these agonists is known to produce enhanced antinociception in several rodent models of acute and chronic pain. The present study investigated the antinociceptive effects of the nonpsychoactive cannabinoid, cannabidiol (CBD) and the μ-opioid agonist morphine, both alone and in combination, using three behavioral models in mice, to test the hypothesis that combinations of morphine and CBD would produce synergistic effects. The effects of morphine, CBD, and morphine/CBD combinations were assessed in the following assays: (a) acetic acid-stimulated stretching; (b) acetic acid-decreased operant responding for palatable food; and (c) hot plate thermal nociception. Morphine alone produced antinociceptive effects in all three models of acute nociception, whereas CBD alone produced antinociception only in the acetic acid-stimulated stretching assay. The nature of the interactions between morphine and CBD combinations were assessed quantitatively based on the principle of dose equivalence. Combinations of CBD and morphine produced synergistic effects in reversing acetic acid-stimulated stretching behavior, but subadditive effects in the hot plate thermal nociceptive assay and the acetic acid-decreased operant responding for palatable food assay. These results suggest that distinct mechanisms of action underlie the interactions between CBD and morphine in the three different behavioral assays and that the choice of appropriate combination therapies for the treatment of acute pain conditions may depend on the underlying pain type and stimulus modality.
PMID:
25485642
DOI:
10.1097/FBP.0000000000000119
[Indexed for MEDLINE]

Anandamide - pain relief

Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism.

Nat Neurosci. 2010 Oct;13(10):1265-70. doi: 10.1038/nn.2632. Epub 2010 Sep 19. **Author information**

Abstract

Peripheral cannabinoid receptors exert a powerful inhibitory control over pain initiation, but the endocannabinoid signal that normally engages this intrinsic analgesic mechanism is unknown. To address this question, we developed a peripherally restricted inhibitor (URB937) of fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of the endocannabinoid anandamide. URB937 suppressed FAAH activity and increased anandamide levels outside the rodent CNS. Despite its inability to access brain and spinal cord, URB937 attenuated behavioral responses indicative of persistent pain in rodent models of peripheral nerve injury and inflammation and prevented noxious stimulus-evoked neuronal activation in spinal cord regions implicated in nociceptive processing. CB_1 cannabinoid receptor blockade prevented these effects. These results suggest that anandamide-mediated signaling at peripheral CB_1 receptors controls the access of pain-related inputs to the CNS. Brain-impenetrant FAAH inhibitors, which strengthen this gating mechanism, might offer a new approach to pain therapy.

Endocannabinoid Deficiency Syndrome

Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes.

Russo EB[1]. (https://www.ncbi.nlm.nih.gov/pubmed/28861491)

Abstract: Medicine continues to struggle in its approaches to numerous common subjective pain syndromes that lack objective signs and remain treatment resistant. Foremost among these are migraine, fibromyalgia, and irritable bowel syndrome, disorders that may overlap in their affected populations and whose sufferers have all endured the stigma of a psychosomatic label, as well as the failure of endless pharmacotherapeutic interventions with substandard benefit. The commonality in symptomatology in these conditions displaying hyperalgesia and central sensitization with possible common underlying pathophysiology suggests that a clinical endocannabinoid deficiency might characterize their origin. Its base hypothesis is that all humans have an underlying endocannabinoid tone that is a reflection of levels of the endocannabinoids, anandamide (arachidonylethanolamide), and 2-arachidonoylglycerol, their production, metabolism, and the relative abundance and state of cannabinoid receptors. Its theory is that in certain conditions, whether congenital or acquired, endocannabinoid tone becomes deficient and productive of pathophysiological syndromes. When first proposed in 2001 and subsequently, this theory was based on genetic overlap and comorbidity, patterns of symptomatology that could be mediated by the endocannabinoid system (ECS), and the fact that exogenous cannabinoid treatment frequently provided symptomatic benefit. However, objective proof and formal clinical trial data were lacking. Currently, however, statistically significant differences in cerebrospinal fluid anandamide levels have been documented in migraineurs, and advanced imaging studies have demonstrated ECS hypofunction in post-traumatic stress disorder. Additional studies have provided a firmer foundation for the theory, while clinical data have also produced evidence for decreased pain, improved sleep, and other benefits to cannabinoid treatment and adjunctive lifestyle approaches affecting the ECS.

Endocannabinoid System: endogenous entourage...

The endogenous fatty acid amide, palmitoylethanolamide [PEA], has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: involvement of CB(1), TRPV1 and PPARgamma receptors and neurotrophic factors.

University of Milano-Bicocca, Italy, 2008 https://www.ncbi.nlm.nih.gov/pubmed/18602217

ABSTRACT: Palmitoylethanolamide (PEA) is an endogenous lipid that is thought to be involved in endogenous protective mechanisms activated as a result of stimulation of inflammatory response. In spite of the well demonstrated anti-inflammatory properties of PEA, its involvement in controlling pain pathways still remains poorly characterized. On this basis, we tested the efficacy of PEA in vivo against a peculiar persistent pain, such as neuropathic one. PEA was administered i.p. to mice with chronic constriction injury of sciatic nerve (CCI) once a day for one week starting the day after the lesion. This therapeutic regimen evoked a relief of both thermal hyperalgesia and mechanical allodynia in neuropathic mice. Various selective receptor antagonists were used in order to clarify the relative contribution of cannabinoid, vanilloid and peroxisome proliferator-activated receptor to PEA-induced effects. The results indicated that CB(1), PPARgamma and TRPV1 receptors mediated the antinociception induced by PEA, suggesting that the most likely mechanism might be the so-called "entourage effect" due to the PEA-induced inhibition of the enzyme catalyzing the endocannabinoid anandamide (AEA) degradation that leads to an enhancement of its tissue levels thus increasing its analgesic action. In addition, the hypothesis that PEA might act through the modulation of local mast cells degranulation is sustained by our findings showing that PEA significantly reduced the production of many mediators such as TNFalpha and neurotrophic factors, like NGF. The findings presented here, in addition to prove the beneficial effects of PEA in chronic pain, identify new potential targets for analgesic medicine.

CBD Acne

“Cannabidiol exerts sebostatic and antiinflammatory effects on human sebocytes.”

https://www.ncbi.nlm.nih.gov/pubmed/25061872 J Clin Invest. 2014 Sep;124(9): 3713-24. doi: 10.1172/JCI64628. Epub 2014 Jul 25.

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

Cannabinoids & Inflammation

“Cannabinoids as novel anti-inflammatory drugs.”

https://www.ncbi.nlm.nih.gov/pubmed/20191092 University of South Carolina, School of Medicine, Future Med Chem. 2009 Oct;1(7):1333-49. doi: 10.4155/fmc.09.93.

Abstract Cannabinoids are a group of compounds that mediate their effects through cannabinoid receptors. The discovery of Δ9-tetrahydrocannabinol (THC) as the major psychoactive principle in marijuana, as well as the identification of cannabinoid receptors and their endogenous ligands, has led to a significant growth in research aimed at understanding the physiological functions of cannabinoids. Cannabinoid receptors include CB1, which is predominantly expressed in the brain, and CB2, which is primarily found on the cells of the immune system. The fact that both CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Recent studies demonstrated that administration of THC into mice triggered marked apoptosis in T cells and dendritic cells, resulting in immunosuppression. In addition, several studies showed that cannabinoids downregulate cytokine and chemokine production and, in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses. The endocannabinoid system is also involved in immunoregulation. For example, administration of endocannabinoids or use of inhibitors of enzymes that break down the endocannabinoids, led to immunosuppression and recovery from immune-mediated injury to organs such as the liver. Manipulation of endocannabinoids and/or use of exogenous cannabinoids in vivo can constitute a potent treatment modality against inflammatory disorders. This review will focus on the potential use of cannabinoids as a new class of anti-inflammatory agents against a number of inflammatory and autoimmune diseases that are primarily triggered by activated T cells or other cellular immune components.

Cannabinoids & Inflammation

“Cannabinoids as novel anti-inflammatory drugs.”

https://www.ncbi.nlm.nih.gov/pubmed/20191092 University of South Carolina, School of Medicine, Future Med Chem. 2009 Oct;1(7):1333-49. doi: 10.4155/fmc.09.93.

CORONARY ARTERY DISEASE: “Cannabidiol has been shown to be effective in protecting endothelial function and integrity in human coronary artery endothelial cells (HCAECs). The study demonstrated that CBD reversed the harmful effects of high glucose on HCAECs by inhibiting [118]:

- Reactive oxygen species production by mitochondria
- NF-κB activation
- Transendothelial migration of monocytes
- Monocyte–endothelial adhesion in HCAECs”

Cannabinoids & Inflammation

“Cannabinoids as novel anti-inflammatory drugs.”

https://www.ncbi.nlm.nih.gov/pubmed/20191092 University of South Carolina, School of Medicine, Future Med Chem. 2009 Oct;1(7):1333-49. doi: 10.4155/fmc.09.93.

EXECUTIVE SUMMARY:

- Cannabinoids, the active components of *Cannabis sativa,* and endogenous cannabinoids mediate their effects through activation of specific cannabinoid receptors known as cannabinoid receptor 1 and 2 (CB1 and CB2).
- The cannabinoid system has been shown both *in vivo* and *in vitro* to be involved in regulating the immune system through its immunomodulatory properties.
- Cannabinoids suppress inflammatory response and subsequently attenuate disease symptoms. This property of cannabinoids is mediated through multiple pathways such as induction of apoptosis in activated immune cells, suppression of cytokines and chemokines at inflammatory sites and upregulation of $FoxP3^{+}$ regulatory T cells.
- Cannabinoids have been tested in several experimental models of autoimmune disorders such as multiple sclerosis, rheumatoid arthritis, colitis and hepatitis and have been shown to protect the host from the pathogenesis through induction of multiple anti-inflammatory pathways.
- Cannabinoids may also be beneficial in certain types of cancers that are triggered by chronic inflammation. In such instances, cannabinoids can either directly inhibit tumor growth or suppress inflammation and tumor angiogenesis.

CBD: pain and inflammation

Mol Brain. 2018 Sep 17;11(1):51. doi: 10.1186/s13041-018-0395-2.

Cannabidiol enhances morphine antinociception, diminishes NMDA-mediated seizures and reduces stroke damage via the sigma 1 receptor.

Rodríguez-Muñoz M1, Onetti Y1, Cortés-Montero E1, Garzón J1, Sánchez-Blázquez P2.
Author information

Abstract
Cannabidiol (CBD), the major non-psychotomimetic compound present in the Cannabis sativa plant, exhibits therapeutic potential for various human diseases, including chronic neurodegenerative diseases, such as Alzheimer's and Parkinson's, ischemic stroke, epilepsy and other convulsive syndromes, neuropsychiatric disorders, neuropathic allodynia and certain types of cancer. CBD does not bind directly to endocannabinoid receptors 1 and 2, and despite research efforts, its specific targets remain to be fully identified. Notably, sigma 1 receptor (σ1R) antagonists inhibit glutamate N-methyl-D-aspartate acid receptor (NMDAR) activity and display positive effects on most of the aforesaid diseases. Thus, we investigated the effects of CBD on three animal models in which NMDAR overactivity plays a critical role: opioid analgesia attenuation, NMDA-induced convulsive syndrome and ischemic stroke. In an in vitro assay, CBD disrupted the regulatory association of σ1R with the NR1 subunit of NMDAR, an effect shared by σ1R antagonists, such as BD1063 and progesterone, and prevented by σ1R agonists, such as 4-IBP, PPCC and PRE084. The in vivo administration of CBD or BD1063 enhanced morphine-evoked supraspinal antinociception, alleviated NMDA-induced convulsive syndrome, and reduced the infarct size caused by permanent unilateral middle cerebral artery occlusion. These positive effects of CBD were reduced by the σ1R agonists PRE084 and PPCC, and absent in σ1R-/- mice. Thus, CBD displays antagonist-like activity toward σ1R to reduce the negative effects of NMDAR overactivity in the abovementioned experimental situations.

KEYWORDS:
Acute pain; Cannabidiol; Cannabinoids; Epilepsy; NMDA receptor; Neuropathology; Sigma 1 receptor; Stroke
PMID: 30223868 PMCID: PMC6142691 DOI: 10.1186/s13041-018-0395-2

CBD: Pan
Pain. 2019 Jan;160(1):136-150. doi: 10.1097/j.pain.0000000000001386.

Cannabidiol modulates serotonergic transmission and reverses both allodynia and anxiety-like behavior in a model of neuropathic pain.

De Gregorio D[1], McLaughlin RJ[2], Posa L[1,3], Ochoa-Sanchez R[1], Enns J[1], Lopez-Canul M[1], Aboud M[1], Maione S[4], Comai S[1,5], Gobbi G[1,3].

Author information

Abstract

Clinical studies indicate that cannabidiol (CBD), the primary nonaddictive component of cannabis that interacts with the serotonin (5-HT)1A receptor, may possess analgesic and anxiolytic effects. However, its effects on 5-HT neuronal activity, as well as its impact on models of neuropathic pain are unknown. First, using in vivo single-unit extracellular recordings in rats, we demonstrated that acute intravenous (i.v.) increasing doses of CBD (0.1-1.0 mg/kg) decreased the firing rate of 5-HT neurons in the dorsal raphe nucleus, which was prevented by administration of the 5-HT1A antagonist WAY 100635 (0.3 mg/kg, i.v.) and the TRPV1 antagonist capsazepine (1 mg/kg, i.v.) but not by the CB1 receptor antagonist AM 251 (1 mg/kg, i.v.). Repeated treatment with CBD (5 mg/kg/day, subcutaneously [s.c.], for 7 days) increased 5-HT firing through desensitization of 5-HT1A receptors. Rats subjected to the spared nerve injury model for 24 days showed decreased 5-HT firing activity, mechanical allodynia, and increased anxiety-like behavior in the elevated plus maze test, open-field test, and novelty-suppressed feeding test. Seven days of treatment with CBD reduced mechanical allodynia, decreased anxiety-like behavior, and normalized 5-HT activity. Antiallodynic effects of CBD were fully prevented by capsazepine (10 mg/kg/day, s.c., for 7 days) and partially prevented by WAY 100635 (2 mg/kg/day, s.c., for 7 days), whereas the anxiolytic effect was blocked only by WAY. Overall, repeated treatment with low-dose CBD induces analgesia predominantly through TRPV1 activation, reduces anxiety through 5-HT1A receptor activation, and rescues impaired 5-HT neurotransmission under neuropathic pain conditions.

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CBD: Pain and Aversion

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Cannabidiol Is a Potential Therapeutic for the Affective-Motivational Dimension of Incision Pain in Rats.

Genaro K[1,2], Fabris D[1,2], Arantes ALF[1,2], Zuardi AW[1,3], Crippa JAS[1,3], Prado WA[2,4].

Abstract

Background: Pain involves different brain regions and is critically determined by emotional processing. Among other areas, the rostral anterior cingulate cortex (rACC) is implicated in the processing of affective pain. Drugs that interfere with the endocannabinoid system are alternatives for the management of clinical pain. Cannabidiol (CBD), a phytocannabinoid found in *Cannabis sativa*, has been utilized in preclinical and clinical studies for the treatment of pain. Herein, we evaluate the effects of CBD, injected either systemically or locally into the rACC, on mechanical allodynia in a postoperative pain model and on the negative reinforcement produced by relief of spontaneous incision pain. Additionally, we explored whether CBD underlies the reward of pain relief after systemic or rACC injection. **Methods and Results:** Male Wistar rats were submitted to a model of incision pain. All rats had mechanical allodynia, which was less intense after intraperitoneal CBD (3 and 10 mg/kg). Conditioned place preference (CPP) paradigm was used to assess negative reinforcement. Intraperitoneal CBD (1 and 3 mg/kg) inverted the CPP produced by peripheral nerve block even at doses that do not change mechanical allodynia. CBD (10 to 40 nmol/0.25 μL) injected into the rACC reduced mechanical allodynia in a dose-dependent manner. CBD (5 nmol/0.25 μL) did not change mechanical allodynia, but reduced peripheral nerve block-induced CPP, and the higher doses inverted the CPP. Additionally, CBD injected systemically or into the rACC at doses that did not change the incision pain evoked by mechanical stimulation significantly produced CPP by itself. Therefore, a non-rewarding dose of CBD in sham-incised rats becomes rewarding in incised rats, presumably because of pain relief or reduction of pain aversiveness. **Conclusion:** The study provides evidence that CBD influences different dimensions of the response of rats to a surgical incision, and the results establish the rACC as a brain area from which CBD evokes antinociceptive effects in a manner similar to the systemic administration of CBD. In addition, the study gives further support to the notion that the sensorial and affective dimensions of pain may be differentially modulated by CBD.

KEYWORDS:
allodynia; anterior cingulate cortex; aversion; cannabidiol; endocannabinoids; pain
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CBD: Chronic Inflammatory and Neuropathic Pain

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The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain.

Costa B[1], Trovato AE, Comelli F, Giagnoni G, Colleoni M.

Abstract

Cannabidiol, the major psycho-inactive component of cannabis, has substantial anti-inflammatory and immunomodulatory effects. This study investigated its therapeutic potential on neuropathic (sciatic nerve chronic constriction) and inflammatory pain (complete Freund's adjuvant intraplantar injection) in rats. In both models, daily oral treatment with cannabidiol (2.5-20 mg/kg to neuropathic and 20 mg/kg to adjuvant-injected rats) from day 7 to day 14 after the injury, or intraplantar injection, reduced hyperalgesia to thermal and mechanical stimuli. In the neuropathic animals, the anti-hyperalgesic effect of cannabidiol (20 mg/kg) was prevented by the vanilloid antagonist capsazepine (10 mg/kg, i.p.), but not by cannabinoid receptor antagonists. Cannabidiol's activity was associated with a reduction in the content of several mediators, such as prostaglandin E(2) (PGE(2)), lipid peroxide and nitric oxide (NO), and in the over-activity of glutathione-related enzymes. Cannabidiol only reduced the over-expression of constitutive endothelial NO synthase (NOS), without significantly affecting the inducible form (iNOS) in inflamed paw tissues. Cannabidiol had no effect on neuronal and iNOS isoforms in injured sciatic nerve. The compound's efficacy on neuropathic pain was not accompanied by any reduction in nuclear factor-kappaB (NF-kappaB) activation and tumor necrosis factor alpha (TNFalpha) content. The results indicate a potential for therapeutic use of cannabidiol in chronic painful states.

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