Evidence for the Putative Cannabinoid Receptor (GPR55)-Mediated Inhibitory Effects on Intestinal Contractility in Mice

Ross G.R. · Lichtman A. · Dewey W.L. · Akbarali H.I.
Keywords: GPR55 · Cannabinoid receptors · JWH015 · Colon contractility · O-1602 · Ileum
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https://doi.org/10.1159/000339076
Abstract

Background: Cannabinoids inhibit intestinal motility via presynaptic cannabinoid receptor type I (CB1) in enteric neurons while cannabinoid receptor type II (CB2) receptors are located mainly in immune cells. The recently de-orphanized G-protein-coupled receptor, GPR55, has been proposed to be the ‘third’ cannabinoid receptor. Although gene expression of GPR55 is evident in the gut, functional evidence for GPR55 in the gut is unknown. In this study, we tested the hypothesis that GPR55 activation inhibits neurogenic contractions in the gut. Methods: We assessed the inhibitory effect of the atypical cannabinoid O-1602, a GPR55 agonist, in mouse colon. Isometric tension recordings in colonic tissue strips were used from either wild-type, GPR55–/– or CB1–/–/CB2–/– knockout mice. Results: O-1602 inhibited the electrical field-induced contractions in the colon strips from wild-type and CB1–/–/CB2–/– in a concentration-dependent manner, suggesting a non-CB1/CB2 receptor-mediated prejunctional effect. The concentration-dependent response of O-1602 was significantly inhibited in GPR55–/– mice. O-1602 did not relax colonic strips precontracted with high K+ (80 mmol/l), indicating no involvement of Ca2+ channel blockade in O-1602-induced relaxation. However, 10 µmol/l O-1602 partially inhibited the exogenous acetylcholine (10 µmol/l)-induced contractions. Moreover, we also assessed the inhibitory effects of JWH015, a CB2/GPR55 agonist on neurogenic contractions of mouse ileum. Surprisingly, the effects of JWH015 were independent of the known cannabinoid receptors. Conclusion: Taken together, these findings suggest that activation of GPR55 leads to inhibition of neurogenic contractions in the gut and are predominantly prejunctal.

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Cannabidiol attenuates alcohol-induced liver steatosis, metabolic dysregulation, inflammation and neutrophil-mediated injury.


Author information

Abstract

Cannabidiol (CBD) is a non-psychoactive component of marijuana, which has anti-inflammatory effects. It has also been approved by FDA for various orphan diseases for exploratory trials. Herein, we investigated the effects of CBD on liver injury induced by chronic plus binge alcohol feeding in mice. CBD or vehicle was administered daily throughout the alcohol feeding study. At the conclusion of the feeding protocol, serum samples, livers or isolated neutrophils were utilized for molecular biology, biochemistry and pathology analysis. CBD significantly attenuated the alcohol feeding-induced serum transaminase elevations, hepatic inflammation (mRNA expressions of TNFα, MCP1, IL1β, MIP2 and E-Selectin, and neutrophil accumulation), oxidative/nitrative stress (lipid peroxidation, 3-nitrotyrosine formation, and expression of reactive oxygen species generating enzyme NOX2). CBD treatment also attenuated the respiratory burst of neutrophils isolated from chronic plus binge alcohol fed mice or from human blood, and decreased the alcohol-induced increased liver triglyceride and fat droplet accumulation. Furthermore, CBD improved alcohol-induced hepatic metabolic dysregulation and steatosis by restoring changes in hepatic mRNA or protein expression of ACC-1, FASN, PPARα, MCAD, ADIPOR-1, and mCPT-1. Thus, CBD may have therapeutic potential in the treatment of alcoholic liver diseases associated with inflammation, oxidative stress and steatosis, which deserves exploration in human trials.

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Free PMC Article
β-Caryophyllene protects against alcoholic steatohepatitis by attenuating inflammation and metabolic dysregulation in mice.

Varga ZV1, Matyas C1, Erdelyi K1, Cinar R2, Nieri D3, Chicca A3, Nemeth BT1, Paloczi J1, Lajtos T1, Corey L1, Hasko G4, Gao B5, Kunos G2, Gertsch J3, Pacher P1.

Abstract

BACKGROUND AND AIMS:
β-Caryophyllene (BCP) is a plant-derived FDA approved food additive with anti-inflammatory properties. Some of its beneficial effects in vivo are reported to involve activation of cannabinoid CB2 receptors that are predominantly expressed in immune cells. Here, we evaluated the translational potential of BCP using a well-established model of chronic and binge alcohol-induced liver injury.

METHODS:
In this study, we investigated the effects of BCP on liver injury induced by chronic plus binge alcohol feeding in mice in vivo by using biochemical assays, real-time PCR and histology analyses. Serum and hepatic BCP levels were also determined by GC/MS.

RESULTS:
Chronic treatment with BCP alleviated the chronic and binge alcohol-induced liver injury and inflammation by attenuating the pro-inflammatory phenotypic `M1` switch of Kupffer cells and by decreasing the expression of vascular adhesion molecules intercellular adhesion molecule 1, E-Selecctin and P-Selectin, as well as the neutrophil infiltration. It also beneficially influenced hepatic metabolic dysregulation (steatosis, protein hyperacetylation and PPAR-α signalling). These protective effects of BCP against alcohol-induced liver injury were attenuated in CB2 receptor knockout mice, indicating that the beneficial effects of this natural product in liver injury involve activation of these receptors. Following acute or chronic administration, BCP was detectable both in the serum and liver tissue homogenates but not in the brain.

CONCLUSIONS:
Given the safety of BCP in humans, this food additive has a high translational potential in treating or preventing hepatic injury associated with oxidative stress, inflammation and steatosis.

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PMCID:
The Cannabinoid Receptor 2 Protects Against Alcoholic Liver Disease Via a Macrophage Autophagy-Dependent Pathway.

Denaës T1,2, Lodder J1,2, Chobert MN1,2, Ruiz I1,2, Pawlotsky JM1,2, Lotersztajn S1,2,3,4, Teixeira-Clerc F1,2.

Author information

Abstract

Kupffer cells, the resident macrophages of the liver, play a major role in the pathogenesis of alcoholic liver disease. We have previously demonstrated that CB2 receptor protects against alcoholic liver disease by inhibiting alcohol-induced inflammation and steatosis via the regulation of Kupffer cell activation. Here, we explored the mechanism underlying these effects and hypothesized that the anti-inflammatory properties of CB2 receptor in Kupffer cells rely on activation of autophagy. For this purpose, mice invalidated for CB2 receptor (CB2(Myel-/-) mice) or for the autophagy gene ATG5 (ATG5(Myel-/-) mice) in the myeloid lineage, and their littermate wild-type mice were subjected to chronic-plus-binge ethanol feeding. CB2(Myel-/-) mice showed exacerbated alcohol-induced pro-inflammatory gene expression and steatosis. Studies in cultured macrophages demonstrated that CB2 receptor activation by JWH-133 stimulated autophagy via a heme oxygenase-1 dependent pathway. Moreover, JWH-133 reduced the induction of inflammatory genes by lipopolysaccharide in wild-type macrophages, but not in ATG5-deficient cells. The CB2 agonist also protected from alcohol-induced liver inflammation and steatosis in wild-type mice, but not in ATG5(Myel-/-) mice demonstrating that macrophage autophagy mediates the anti-inflammatory and anti-steatogenic effects of CB2 receptor.

Altogether these results demonstrate that CB2 receptor activation in macrophages protects from alcohol-induced steatosis by inhibiting hepatic inflammation through an autophagy-dependent pathway.

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Free PMC Article
Cannabinoid CB2 receptors protect against alcoholic liver disease by regulating Kupffer cell polarization in mice.


Abstract
Activation of Kupffer cells plays a central role in the pathogenesis of alcoholic liver disease. Because cannabinoid CB2 receptors (CB2) display potent anti-inflammatory properties, we investigated their role in the pathogenesis of alcoholic liver disease, focusing on the impact of CB2 on Kupffer cell polarization and the consequences on liver steatosis. Wild-type (WT) mice fed an alcohol diet showed an induction of hepatic classical (M1) and alternative (M2) markers. Cotreatment of alcohol-fed mice with the CB2 agonist, JWH-133, decreased hepatic M1 gene expression without affecting the M2 profile. In keeping with this, genetic ablation of CB2 enhanced hepatic induction of M1 gene signature and blunted the induction of M2 markers. CB2 also modulated alcohol-induced fatty liver, as shown by the reduction of hepatocyte steatosis in JWH-133-treated mice and its enhancement in CB2-/- animals. Studies in isolated Kupffer cells and cultured macrophages further demonstrated that CB2 inhibits M1 polarization and favors the transition to an M2 phenotype. In addition, conditioned-medium experiments showed that preventing M1 polarization in CB2-activated macrophages protects from lipid accumulation in hepatocytes. Heme oxygenase-1 (HO-1) mediated the anti-inflammatory effects of CB2 receptors. Indeed, alcohol-fed mice treated with JWH-133 showed increased hepatic expression of macrophage HO-1, as compared to vehicle-treated counterparts. In keeping with this, JWH-133 induced HO-1 expression in cultured macrophages, and the HO-1 inhibitor, zinc protoporphyrin, blunted the inhibitory effect of JWH-133 on lipopolysaccharide-induced nuclear factor-kappa B activation and M1 polarization. Altogether, these findings demonstrate that CB2 receptors display beneficial effects on alcohol-induced inflammation by regulating M1/M2 balance in Kupffer cells, thereby reducing hepatocyte steatosis via paracrine interactions between Kupffer cells and hepatocytes. These data identify CB2 agonists as potential therapeutic agents for the management of alcoholic liver disease.

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DOI: 10.1002/hep.24524
Mechanistic Potential and Therapeutic Implications of Cannabinoids in Nonalcoholic Fatty Liver Disease.

Dibba P1, Li A2, Cholankeril G3, Iqbal U4, Gadiparthi C5, Khan MA6, Kim D7, Ahmed A8.

Author information

Abstract
Nonalcoholic fatty liver disease (NAFLD) is comprised of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). It is defined by histologic or radiographic evidence of steatosis in the absence of alternative etiologies, including significant alcohol consumption, steatogenic medication use, or hereditary disorders. NAFLD is now the most common liver disease, and when NASH is present it can progress to fibrosis and hepatocellular carcinoma. Different mechanisms have been identified as contributors to the physiology of NAFLD; insulin resistance and related metabolic derangements have been the hallmark of physiology associated with NAFLD. The mainstay of treatment has classically involved lifestyle modifications focused on the reduction of insulin resistance. However, emerging evidence suggests that the endocannabinoid system and its associated cannabinoid receptors and ligands have mechanistic and therapeutic implications in metabolic derangements and specifically in NAFLD. Cannabinoid receptor 1 antagonism has demonstrated promising effects with increased resistance to hepatic steatosis, reversal of hepatic steatosis, and improvements in glycemic control, insulin resistance, and dyslipidemia. Literature regarding the role of cannabinoid receptor 2 in NAFLD is controversial. Exocannabinoids and endocannabinoids have demonstrated some therapeutic impact on metabolic derangements associated with NAFLD, although literature regarding direct therapeutic use in NAFLD is limited. Nonetheless, the properties of the endocannabinoid system, its receptors, substrates, and ligands remain a significant arena warranting further research, with potential for a pharmacologic intervention for a disease with an anticipated increase in economic and clinical burden.

KEYWORDS:
NAFLD; NASH; cannabinoids; endocannabinoid; endocannabinoid system; exocannabinoid; nonalcoholic fatty liver disease; nonalcoholic steatohepatitis

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Free PMC Article
Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes.

Jiang R1, Yamaori S, Takeda S, Yamamoto I, Watanabe K.

Abstract
AIMS: Cannabidiol (CBD), one of the major constituents in marijuana, has been shown to be extensively metabolized by experimental animals and humans. However, human hepatic enzymes responsible for the CBD metabolism remain to be elucidated. In this study, we examined in vitro metabolism of CBD with human liver microsomes (HLMs) to clarify cytochrome P450 (CYP) isoforms involved in the CBD oxidations.

MAIN METHODS: Oxidations of CBD in HLMs and recombinant human CYP enzymes were analyzed by gas chromatography/mass spectrometry.

KEY FINDINGS: CBD was metabolized by pooled HLMs to eight monohydroxylated metabolites (6α-OH-, 6β-OH-, 7-OH-, 1″-OH-, 2″-OH-, 3″-OH-, 4″-OH-, and 5″-OH-CBDs). Among these metabolites, 6α-OH-, 6β-OH-, 7-OH-, and 4″-OH-CBDs were the major ones as estimated from the relative abundance of m/z 478, which was a predominant fragment ion of trimethylsilyl derivatives of the metabolites. Seven of 14 recombinant human CYP enzymes examined (CYP1A1, CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, and CYP3A5) were capable of metabolizing CBD. The correlations between CYP isoform-specific activities and CBD oxidative activities in 16 individual HLMs indicated that 6β-OH- and 4″-OH-CBDs were mainly formed by CYP3A4, which was supported by inhibition studies using ketoconazole and an anti-CYP3A4 antibody. The correlation and inhibition studies also showed that CBD 6α-hydroxylation was mainly catalyzed by CYP3A4 and CYP2C19, whereas CBD 7-hydroxylation was predominantly catalyzed by CYP2C19.

SIGNIFICANCE: This study indicated that CBD was extensively metabolized by HLMs. These results suggest that CYP3A4 and CYP2C19 may be major isoforms responsible for 6α-, 6β-, 7-, and/or 4″-hydroxylations of CBD in HLMs.

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Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis.


Abstract

Enteric glial cells (EGC) actively mediate acute and chronic inflammation in the gut; EGC proliferate and release neurotrophins, growth factors, and pro-inflammatory cytokines which, in turn, may amplify the immune response, representing a very important link between the nervous and immune systems in the intestine. Cannabidiol (CBD) is an interesting compound because of its ability to control reactive gliosis in the CNS, without any unwanted psychotropic effects. Therefore the rationale of our study was to investigate the effect of CBD on intestinal biopsies from patients with ulcerative colitis (UC) and from intestinal segments of mice with LPS-induced intestinal inflammation. CBD markedly counteracted reactive enteric gliosis in LPS-mice through the massive reduction of astroglial signalling neurotrophin S100B. Histological, biochemical and immunohistochemical data demonstrated that S100B decrease was associated with a considerable decrease in mast cell and macrophages in the intestine of LPS-treated mice after CBD treatment. Moreover the treatment of LPS-mice with CBD reduced TNF-α expression and the presence of cleaved caspase-3. Similar results were obtained in ex vivo cultured human derived colonic biopsies. In biopsies of UC patients, both during active inflammation and in remission stimulated with LPS+INF-γ, an increased glial cell activation and intestinal damage were evidenced. CBD reduced the expression of S100B and iNOS proteins in the human biopsies confirming its well documented effect in septic mice. The activity of CBD is, at least partly, mediated via the selective PPAR-gamma receptor pathway. CBD targets enteric reactive gliosis, counteracts the inflammatory environment induced by LPS in mice and in human colonic cultures derived from UC patients. These actions lead to a reduction of intestinal damage mediated by PPARgamma receptor pathway. Our results therefore indicate that CBD indeed unravels a new therapeutic strategy to treat inflammatory bowel diseases.
Cannabidiol in inflammatory bowel diseases: a brief overview.

Esposito G1, Filippis DD, Cirillo C, Iuvone T, Capoccia E, Scuderi C, Steardo A, Cuomo R, Steardo L.

Abstract

This minireview 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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DOI: 10.1002/ptr.4781
[Indexed for MEDLINE]
Irritable Bowel Syndrome / Disease - CBC

- “Inhibitory effect of cannabichromene [CBC], a major non-psychotropic cannabinoid extracted from Cannabis sativa, on inflammation-induced hypermotility in mice.


- **ABSTRACT:** BACKGROUND AND PURPOSE: Cannabichromene (CBC) is a major non-psychotropic phytocannabinoid that inhibits endocannabinoid inactivation and activates the transient receptor potential ankyrin-1 (TRPA1). Both endocannabinoids and TRPA1 may modulate gastrointestinal motility. Here, we investigated the effect of CBC on mouse intestinal motility in physiological and pathological states.

  - **EXPERIMENTAL APPROACH:** Inflammation was induced in the mouse small intestine by croton oil. Endocannabinoid (anandamide and 2-arachidonoyl glycerol), palmitoylethanolamide and oleoylethanolamide levels were measured by liquid chromatography-mass spectrometry; TRPA1 and cannabinoid receptors were analysed by quantitative RT-PCR; upper gastrointestinal transit, colonic propulsion and whole gut transit were evaluated in vivo; contractility was evaluated in vitro by stimulating the isolated ileum, in an organ bath, with ACh or electrical field stimulation (EFS).

  - **KEY RESULTS:** Croton oil administration was associated with decreased levels of anandamide (but not 2-arachidonoyl glycerol) and palmitoylethanolamide, up-regulation of TRPA1 and CB₁ receptors and down-regulation of CB₂ receptors. Ex vivo CBC did not change endocannabinoid levels, but it altered the mRNA expression of TRPA1 and cannabinoid receptors. In vivo, CBC did not affect motility in control mice, but normalized croton oil-induced hypermotility. In vitro, CBC reduced preferentially EFS- versus ACh-induced contractions. Both in vitro and in vivo, the inhibitory effect of CBC was not modified by cannabinoid or TRPA1 receptor antagonists.

  - **CONCLUSION AND IMPLICATIONS:** CBC selectively reduces inflammation-induced hypermotility in vivo in a manner that is not dependent on cannabinoid receptors or TRPA1.
Inflammatory Bowel Disease -- CBG


- **Abstract** Inflammatory bowel disease (IBD) is an incurable disease which affects millions of people in industrialized countries. Anecdotal and scientific evidence suggests that Cannabis use may have a positive impact in IBD patients. Here, we investigated the effect of cannabigerol (CBG), a non-psychotropic Cannabis-derived cannabinoid, in a murine model of colitis. Colitis was induced in mice by intracolonic administration of dinitrobenzene sulphonate acid (DNBS). Inflammation was assessed by evaluating inflammatory markers/parameters (colon weight/colon length ratio and myeloperoxidase activity), by histological analysis and immunohistochemistry; interleukin-1β, interleukin-10 and interferon-γ levels by ELISA, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) by western blot and RT-PCR; CuZn-superoxide dismutase (SOD) activity by a colorimetric assay. Murine macrophages and intestinal epithelial cells were used to evaluate the effect of CBG on nitric oxide production and oxidative stress, respectively. CBG reduced colon weight/colon length ratio, myeloperoxidase activity, and iNOS expression, increased SOD activity and normalized interleukin-1β, interleukin-10 and interferon-γ changes associated to DNBS administration. In macrophages, CBG reduced nitric oxide production and iNOS protein (but not mRNA) expression. Rimonabant (a CB1 receptor antagonist) did not change the effect of CBG on nitric oxide production, while SR144528 (a CB2 receptor antagonist) further increased the inhibitory effect of CBG on nitric oxide production. In conclusion, CBG attenuated murine colitis, reduced nitric oxide production in macrophages (effect being modulated by the CB2 receptor) and reduced ROS formation in intestinal epithelial cells. CBG could be considered for clinical experimentation in IBD patients. (blue = entourage effect)

- CONTROLS COLITIS, elicits entourage effect.
IBD / Colitis : THC, CBD, and THC+CBD

“The effects of Delta-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis.”

University of Hertfordshire, Hatfield, Hertfordshire, UK. https://www.ncbi.nlm.nih.gov/pubmed/20590574

ABSTRACT: BACKGROUND AND PURPOSE: Cannabis is taken as self-medication by patients with inflammatory bowel disease for symptomatic relief. Cannabinoid receptor agonists decrease inflammation in animal models of colitis, but their effects on the disturbed motility is not known. (-)-Cannabidiol (CBD) has been shown to interact with Delta(9)-tetrahydrocannabinol (THC) in behavioural studies, but it remains to be established if these cannabinoids interact in vivo in inflammatory disorders. Therefore the effects of CBD and THC alone and in combination were investigated in a model of colitis.

KEY RESULTS: Sulphasalazine, THC and CBD proved beneficial in this model of colitis with the dose-response relationship for the phytocannabinoids showing a bell-shaped pattern on the majority of parameters (optimal THC and CBD dose, 10 mg.kg(-1)). THC was the most effective drug. The effects of these phytocannabinoids were additive, and CBD increased some effects of an ineffective THC dose to the level of an effective one. THC alone and in combination with CBD protected cholinergic nerves whereas sulphasalazine did not.

CONCLUSIONS AND IMPLICATIONS: In this model of colitis, THC and CBD not only reduced inflammation but also lowered the occurrence of functional disturbances. Moreover the combination of CBD and THC could be beneficial therapeutically, via additive or potentiating effects.
Inflammatory Bowel Disease -- CBD “Cannabidiol in inflammatory bowel diseases: a brief overview.”

Sapienza University of Rome 2013: https://www.ncbi.nlm.nih.gov/pubmed/22815234

ABSTRACT: This minireview 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.
Appendicitis and Colitis: CBD
Cannabidiol [CBD] and palmitoylethanolamide [PEA] are anti-inflammatory in the acutely inflamed human colon.

University of Nottingham, 2017 https://www.ncbi.nlm.nih.gov/pubmed/28954820

ABSTRACT: OBJECTIVE: We sought to quantify the anti-inflammatory effects of two cannabinoid drugs, cannabidiol (CBD) and palmitoylethanolamide (PEA), in cultured cell lines and compared this effect with experimentally inflamed explant human colonic tissue. These effects were explored in acutely and chronically inflamed colon, using inflammatory bowel disease and appendicitis explants.

DESIGN: Caco-2 cells and human colonic explants collected from elective bowel cancer, inflammatory bowel disease (IBD) or acute appendicitis resections, and were treated with the following drug treatments: vehicle, an inflammatory protocol of interferon γ (IFNγ) and tumour necrosis factor α (TNFα; 10 ng/ml), inflammation and PEA (10 μM), inflammation and CBD (10 μM), and PEA or CBD alone, CBD or vehicle were added simultaneously with IFNγ.

RESULTS: IFNγ and TNFα treatment increased phosphoprotein and cytokine levels in Caco-2 cultures and colonic explants. Phosphoprotein levels were significantly reduced by PEA or CBD in Caco-2 cultures and colonic explants. CBD and PEA prevented increases in cytokine production in explant colon, but not in Caco-2 cells. CBD effects were blocked by the CB2 antagonist AM630 and TRPV1 antagonist SB366791. PEA effects were blocked by the PPARα antagonist GW6471. PEA and CBD were anti-inflammatory in IBD and appendicitis explants.

CONCLUSION: PEA and CBD are anti-inflammatory in the human colon. This effect is not seen in cultured epithelial cells. Appropriately sized clinical trials should assess their efficacy.
Chron’s Colitis: CBD needs its entourage...

Low-Dose Cannabidiol [10mg oral CBD] Is Safe but Not Effective in the Treatment for Crohn's Disease, a Randomized Controlled Trial.

Tel Aviv 2017: https://www.ncbi.nlm.nih.gov/pubmed/28349233

ABSTRACT: BACKGROUND: Cannabidiol (CBD) is an anti-inflammatory cannabinoid shown to be beneficial in a mouse model of IBD. Lacking any central effect, cannabidiol is an attractive option for treating inflammatory diseases.

AIM: To assess the effects of cannabidiol on Crohn's disease in a randomized placebo-controlled trial.

PATIENTS AND METHODS: Twenty patients aged 18-75 years with a Crohn’s disease activity index (CDAI) >200 were randomized to receive oral (10 mg) CBD or placebo twice daily. Patients did not respond to standard treatment with steroids (11 patients), thiopurines (14), or TNF antagonists (11). Disease activity and laboratory parameters were assessed during 8 weeks of treatment and 2 weeks thereafter. Other medical treatment remained unchanged.

RESULTS: Of 20 patients recruited 19 completed the study. Their mean age was 39 ± 15, and 11 were males. The average CDAI before cannabidiol consumption was 337 ± 108 and 308 ± 96 (p = NS) in the CBD and placebo groups, respectively. After 8 weeks of treatment, the index was 220 ± 122 and 216 ± 121 in the CBD and placebo groups, respectively (p = NS). Hemoglobin, albumin, and kidney and liver function tests remained unchanged. No side effects were observed.

CONCLUSION: In this study of moderately active Crohn's disease, CBD was safe but had no beneficial effects. This could be due to lack of effect of CBD on Crohn's disease, but could also be due to the small dose of CBD, the small number of patients in the study, or the lack of the necessary synergism with other cannabinoids. Further investigation is warranted.

KEYWORDS: Cannabidiol; Cannabis; Crohn’s disease; Inflammatory bowel disease
IBD / Colitis: PCR Hemp (termed “CBD BDS” here)

An Orally Active Cannabis Extract with High Content in Cannabidiol [CBD BDS] attenuates Chemically-induced Intestinal Inflammation and Hypermotility in the Mouse.


ABSTRACT: Anecdotal and scientific evidence suggests that Cannabis use may be beneficial in inflammatory bowel disease (IBD) patients. Here, we have investigated the effect of a standardized Cannabis sativa extract with high content of cannabidiol (CBD), here named CBD BDS for “CBD botanical drug substance,” on mucosal inflammation and hypermotility in mouse models of intestinal inflammation. Colitis was induced in mice by intracolonic administration of dinitrobenzenesulfonic acid (DNBS). Motility was evaluated in the experimental model of intestinal hypermotility induced by irritant croton oil. CBD BDS or pure CBD were given - either intraperitoneally or by oral gavage - after the inflammatory insult (curative protocol). The amounts of CBD in the colon, brain, and liver after the oral treatments were measured by high-performance liquid chromatography coupled to ion trap-time of flight mass spectrometry. CBD BDS, both when given intraperitoneally and by oral gavage, decreased the extent of the damage (as revealed by the decrease in the colon weight/length ratio and myeloperoxidase activity) in the DNBS model of colitis. It also reduced intestinal hypermotility (at doses lower than those required to affect transit in healthy mice) in the croton oil model of intestinal hypermotility. Under the same experimental conditions, pure CBD did not ameliorate colitis while it normalized croton oil-induced hypermotility when given intraperitoneally (in a dose-related fashion) or orally (only at one dose). In conclusion, CBD BDS, given after the inflammatory insult, attenuates injury and motility in intestinal models of inflammation. These findings sustain the rationale of combining CBD with other minor Cannabis constituents and support the clinical development of CBD BDS for IBD treatment.
ABSTRACT: Modulating the activity of the endocannabinoid system influences various gastrointestinal physiological and pathophysiological processes, and cannabinoid receptors as well as regulatory enzymes responsible for the synthesis or degradation of endocannabinoids representing potential targets to reduce the development of gastrointestinal mucosal lesions, hemorrhage and inflammation. Direct activation of CB₁ receptors by plant-derived, endogenous or synthetic cannabinoids effectively reduces both gastric acid secretion and gastric motor activity, and decreases the formation of gastric mucosal lesions induced by stress, pylorus ligation, nonsteroidal anti-inflammatory drugs (NSAIDs) or alcohol, partly by peripheral, partly by central mechanisms. Similarly, indirect activation of cannabinoid receptors through elevation of endocannabinoid levels by globally acting or peripherally restricted inhibitors of their metabolizing enzymes (FAAH, MAGL) or by inhibitors of their cellular uptake reduces the gastric mucosal lesions induced by NSAIDs in a CB₁ receptor-dependent fashion. Dual inhibition of FAAH and cyclooxygenase enzymes induces protection against both NSAID-induced gastrointestinal damage and intestinal inflammation. Moreover, in intestinal inflammation direct or indirect activation of CB₁ and CB₂ receptors exerts also multiple beneficial effects. Namely, activation of both CB receptors was shown to ameliorate intestinal inflammation in various murine colitis models, to decrease visceral hypersensitivity and abdominal pain, as well as to reduce colitis-associated hypermotility and diarrhea. In addition, CB₁ receptors suppress secretory processes and also modulate intestinal epithelial barrier functions. Thus, experimental data suggest that the endocannabinoid system represents a promising target in the treatment of inflammatory bowel diseases, and this assumption is also confirmed by preliminary clinical studies.
Bioperine and Capsacin

Effect of vanilloid drugs on gastrointestinal transit in mice.


Abstract: We have studied the effect of capsaicin, piperine and anandamide, drugs which activate vanilloid receptors and capsazepine, a vanilloid receptor antagonist, on upper gastrointestinal motility in mice. 2. Piperine (0.5 - 20 mg kg(-1) i.p.) and anandamide (0.5 - 20 mg kg(-1) i.p.), dose-dependently delayed gastrointestinal motility, while capsaicin (up to 3 mg kg(-1) i.p.) was without effect. Capsazepine (15 mg kg(-1) i.p.) neither per se affected gastrointestinal motility nor did it counteract the inhibitory effect of both piperine (10 mg kg(-1)) and anandamide (10 mg kg(-1)). 3. A per se non effective dose of SR141716A (0.3 mg kg(-1) i.p.), a cannabinoid CB(1) receptor antagonist, counteracted the inhibitory effect of anandamide (10 mg kg(-1)) but not of piperine (10 mg kg(-1)). By contrast, the inhibitory effect of piperine (10 mg kg(-1)) but not of anandamide (10 mg kg(-1)) was strongly attenuated in capsaicin (75 mg kg(-1) in total, s.c.)-treated mice. 4. Pretreatment of mice with N(G)-nitro-L-arginine methyl ester (25 mg kg(-1) i.p.), yohimbine (1 mg kg(-1), i.p.), naloxone (2 mg kg(-1) i.p.), or hexamethonium (1 mg kg(-1) i.p.) did not modify the inhibitory effect of both piperine (10 mg kg(-1)) and anandamide (10 mg kg(-1)). 5. The present study indicates that the vanilloid ligands anandamide and piperine, but not capsaicin, can reduce upper gastrointestinal motility. The effect of piperine involves capsaicin-sensitive neurones, but not vanilloid receptors, while the effect of anandamide involves cannabinoid CB(1), but not vanilloid receptors.
CBD: protects liver from NASH (Metabolic Syndrome)

Mechanistic Potential and Therapeutic Implications of Cannabinoids in Nonalcoholic Fatty Liver Disease.

Dibba P1, Li A2, Cholankeril G3, Iqbal U4, Gadiparthi C5, Khan MA6, Kim D7, Ahmed A8.

Abstract
Nonalcoholic fatty liver disease (NAFLD) is comprised of nonalcoholic fatty liver (NAFL) and nonalcoholic steatohepatitis (NASH). It is defined by histologic or radiographic evidence of steatosis in the absence of alternative etiologies, including significant alcohol consumption, steatogenic medication use, or hereditary disorders. NAFLD is now the most common liver disease, and when NASH is present it can progress to fibrosis and hepatocellular carcinoma. Different mechanisms have been identified as contributors to the physiology of NAFLD; insulin resistance and related metabolic derangements have been the hallmark of physiology associated with NAFLD. The mainstay of treatment has classically involved lifestyle modifications focused on the reduction of insulin resistance. However, emerging evidence suggests that the endocannabinoid system and its associated cannabinoid receptors and ligands have mechanistic and therapeutic implications in metabolic derangements and specifically in NAFLD. Cannabinoid receptor 1 antagonism has demonstrated promising effects with increased resistance to hepatic steatosis, reversal of hepatic steatosis, and improvements in glycemic control, insulin resistance, and dyslipidemia. Literature regarding the role of cannabinoid receptor 2 in NAFLD is controversial. Exocannabinoids and endocannabinoids have demonstrated some therapeutic impact on metabolic derangements associated with NAFLD, although literature regarding direct therapeutic use in NAFLD is limited. Nonetheless, the properties of the endocannabinoid system, its receptors, substrates, and ligands remain a significant arena warranting further research, with potential for a pharmacologic intervention for a disease with an anticipated increase in economic and clinical burden.

KEYWORDS:
NAFLD; NASH; cannabinoids; endocannabinoid; endocannabinoid system; exocannabinoid; nonalcoholic fatty liver disease; nonalcoholic steatohepatitis

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Free PMC Article
CBD: Irritable Bowel / Intestinal Contractility


The effects of cannabidiolic acid and cannabidiol on contractility of the gastrointestinal tract of Suncus murinus.

Cluny NL¹, Naylor RJ, Whittle BA, Javid FA.

Author information

Abstract

Cannabidiol (CBD) has been shown to inhibit gastrointestinal (GI) transit in pathophysiologic in vivo models, while having no effect in physiologic controls. The actions of the precursor of CBD, cannabidiolic acid (CBDA), have not been investigated in the GI tract. The actions of these phytocannabinoids on the contractility of the GI tract of Suncus murinus were investigated in the current study. The effects of CBDA and CBD in resting state and pre-contracted isolated intestinal segments, and on the contractile effects of carbachol and electrical field stimulation (EFS) on the intestines of S. murinus were examined. CBDA and CBD induced a reduction in resting tissue tension of isolated intestinal segments which was not blocked by the cannabinoid CB1 receptor antagonist, AM251, the CB(2) receptor antagonist AM630, or tetrodotoxin. CBDA and CBD reduced the magnitude of contractions induced by carbachol and the tension of intestinal segments that were pre-contracted with potassium chloride. In tissues stimulated by EFS, CBDA inhibited contractions induced by lower frequencies (0.1-4.0 Hz) of EFS, while CBD inhibited contractions induced by higher frequencies (4.0-20.0 Hz) of EFS. The data suggest that CBDA and CBD have inhibitory actions on the intestines of S. murinus that are not neuronallymediated or mediated via CB(1) or CB(2) receptors.

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CBD: serotonin = “happy gut”


Cannabidiolic acid prevents vomiting in Suncus murinus and nausea-induced behaviour in rats by enhancing 5-HT1A receptor activation.

Bolognini D1, Rock EM, Cluny NL, Cascio MG, Limebeer CL, Duncan M, Stott CG, Javid FA, Parker LA, Pertwee RG.

Abstract

BACKGROUND AND PURPOSE:
To evaluate the ability of cannabidiolic acid (CBDA) to reduce nausea and vomiting and enhance 5-HT(1A) receptor activation in animal models.

EXPERIMENTAL APPROACH:
We investigated the effect of CBDA on (i) lithium chloride (LiCl)-induced conditioned gaping to a flavour (nausea-induced behaviour) or a context (model of anticipatory nausea) in rats; (ii) saccharin palatability in rats; (iii) motion-, LiCl- or cisplatin-induced vomiting in house musk shrews (Suncus murinus); and (iv) rat brainstem 5-HT(1A) receptor activation by 8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) and mouse whole brain CB(1) receptor activation by CP55940, using [55S]GTPγS-binding assays.

KEY RESULTS:
In shrews, CBDA (0.1 and/or 0.5 mg·kg⁻¹ i.p.) reduced toxin- and motion-induced vomiting, and increased the onset latency of the first motion-induced emetic episode. In rats, CBDA (0.01 and 0.1 mg·kg⁻¹ i.p.) suppressed LiCl- and context-induced conditioned gaping, effects that were blocked by the 5-HT(1A) receptor antagonist, WAY100635 (0.1 mg·kg⁻¹ i.p.), and, at 0.01 mg·kg⁻¹ i.p., enhanced saccharin palatability. CBDA-induced suppression of LiCl-induced conditioned gaping was unaffected by the CB₁ receptor antagonist, SR141716A (1 mg·kg⁻¹ i.p.). In vitro, CBDA (0.1-100 nM) increased the E(max) of 8-OH-DPAT.

CONCLUSIONS AND IMPLICATIONS:
Compared with cannabidiol, CBDA displays significantly greater potency at inhibiting vomiting in shrews and nausea in rats, and at enhancing 5-HT(1A) receptor activation, an action that accounts for its ability to attenuate conditioned gaping in rats. Consequently, CBDA shows promise as a treatment for nausea and vomiting, including anticipatory nausea for which no specific therapy is currently available.


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Cannabis for inflammatory bowel disease.

Naftali T, Mechulam R, Lev LB, Konikoff FM.

Author information

Abstract

The marijuana plant Cannabis sativa has been used for centuries as a treatment for a variety of ailments. It contains over 60 different cannabinoid compounds. Studies have revealed that the endocannabinoid system is involved in almost all major immune events. Cannabinoids may, therefore, be beneficial in inflammatory disorders. In murine colitis, cannabinoids decrease histologic and microscopic inflammation. In humans, cannabis has been used to treat a plethora of gastrointestinal problems, including anorexia, emesis, abdominal pain, diarrhea, and diabetic gastroparesis. Despite anecdotal reports on medical cannabis in inflammatory bowel disease (IBD), there are few controlled studies. In an observational study in 30 patients with Crohn's disease (CD), we found that medical cannabis was associated with improvement in disease activity and reduction in the use of other medications. In a more recent placebo-controlled study in 21 chronic CD patients, we showed a decrease in the CD activity index >100 in 10 of 11 subjects on cannabis compared to 4 of 10 on placebo. Complete remission was achieved in 5 of 11 subjects in the cannabis group and 1 of 10 in the placebo group. Yet, in an additional study, low-dose cannabidiol did not have an effect on CD activity. In summary, evidence is gathering that manipulating the endocannabinoid system can have beneficial effects in IBD, but further research is required to declare cannabinoids a medicine. We need to establish the specific cannabinoids, as well as appropriate medical conditions, optimal dose, and mode of administration, to maximize the beneficial effects while avoiding any potential harmful effects of cannabinoid use.

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