CBD: alcohol

Pharmacol Biochem Behav. 2013 Oct;111:120-7. doi: 10.1016/j.pbb.2013.08.013. Epub 2013 Sep 5.

Transdermal delivery of cannabidiol attenuates binge alcohol-induced neurodegeneration in a rodent model of an alcohol use disorder.

Liput DJ1, Hammell DC, Stinchcomb AL, Nixon K.
Author information

Erratum in
Pharmacol Biochem Behav. 2014 Nov;126:187-8.

Abstract
Excessive alcohol consumption, characteristic of alcohol use disorders, results in neurodegeneration and behavioral and cognitive impairments that are hypothesized to contribute to the chronic and relapsing nature of alcoholism. Therefore, the current study aimed to advance the preclinical development of transdermal delivery of cannabidiol (CBD) for the treatment of alcohol-induced neurodegeneration. In Experiment 1, 1.0%, 2.5% and 5.0% CBD gels were evaluated for neuroprotection. The 5.0% CBD gel resulted in a 48.8% reduction in neurodegeneration in the entorhinal cortex assessed by Fluoro-Jade B (FJB), which trended to statistical significance (p=0.069). Treatment with the 5.0% CBD gel resulted in day 3 CBD plasma concentrations of ~100.0 ng/mL so this level was used as a target concentration for development of an optimized gel formulation. Experiment 2 tested a next generation 2.5% CBD gel formulation, which was compared to CBD administration by intraperitoneal injection (IP; 40.0 mg/kg/day). This experiment found similar magnitudes of neuroprotection following both routes of administration; transdermal CBD decreased FJB+ cells in the entorhinal cortex by 56.1% ($p<0.05$), while IP CBD resulted in a 50.6% ($p<0.05$) reduction in FJB+ cells. These results demonstrate the feasibility of using CBD transdermal delivery systems for the treatment of alcohol-induced neurodegeneration.

KEYWORDS:
Alcoholism; Cannabidiol; Ethanol; Neuroprotection; Neurotoxicity; Transdermal
PMID:
24012796
PMCID:
PMC4096899
DOI:
10.1016/j.pbb.2013.08.013

CBD: alcohol damage

Sci Rep. 2017 Sep 21;7(1):12064. doi: 10.1038/s41598-017-10924-8.

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

Wang Y1,2, Mukhopadhyay P1, Cao Z1, Wang H3, Feng D3, Haskó G4, Mechoulam R5, Gao B3, Pacher P6.
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, serums 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.

PMID:
28935932
PMCID:
PMC5608708
DOI:
10.1038/s41598-017-10924-8
Free PMC Article

Caryophyllene: (a terpene prevalent in PoP tablets) protects liver from alcohol damage

Br J Pharmacol. 2018 Jan;175(2): 320-334. doi: 10.1111/bph.13722. Epub 2017 Feb 22.

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.
Author information

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-Selectin 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.
LINKED ARTICLES:
This article is part of a themed section on Inventing New Therapies Without Reinventing the Wheel: The Power of Drug Repurposing. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v175.2/issuetoc.

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28107775
PMCID:
PMC5758392
[Available on 2019-01-01]
DOI:
10.1111/bph.13722
[Indexed for MEDLINE]
Free full text

CBD: Liver damage from alcohol

Sci Rep. 2016 Jun 27;6:28806. doi: 10.1038/srep28806.

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(Mye-/-) mice) or for the autophagy gene ATG5 (ATG5(Mye-/-) mice) in the myeloid lineage, and their littermate wild-type mice were subjected to chronic-plus-binge ethanol feeding. CB2(Mye-/-) 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(Mye-/-) 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.

PMID:
27346657
PMCID:
PMC4921859
DOI:
10.1038/srep28806
[Indexed for MEDLINE]
Free PMC Article

CBD: protects liver from alcohol damage

Hepatology. 2011 Oct;54(4):1217-26. doi: 10.1002/hep.24524. Epub 2011 Sep 6.

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

Louvet A1, Teixeira-Clerc F, Chobert MN, Deveaux V, Pavoine C, Zimmer A, Pecker F, Mallat A, Lotersztajn S.
Author information

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.

PMID:
21735467
DOI:
10.1002/hep.24524

CBD: safe with, and protects from, Fentanyl

J Addict Med. 2015 May-Jun;9(3):204-10. doi: 10.1097/ADM.0000000000000118.

Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans.

Manini AF1, Yiannoulos G, Bergamaschi MM, Hernandez S, Olmedo R, Barnes AJ, Winkel G, Sinha R, Jutras-Aswad D, Huestis MA, Hurd YL.
Author information

Abstract
OBJECTIVES:
Cannabidiol (CBD) is hypothesized as a potential treatment for opioid addiction, with safety studies an important first step for medication development. We determined CBD safety and pharmacokinetics when administered concomitantly with a high-potency opioid in healthy subjects.
METHODS:
This double-blind, placebo-controlled cross-over study of CBD, coadministered with intravenous fentanyl, was conducted at the Clinical Research Center in Mount Sinai Hospital, a tertiary care medical center in New York City. Participants were healthy volunteers aged 21 to 65 years with prior opioid exposure, regardless of the route. Blood samples were obtained before and after 400 or 800 mg of CBD pretreatment, followed by a single 0.5 (session 1) or 1.0 μg/kg (session 2) of intravenous fentanyl dose. The primary outcome was the Systematic Assessment for Treatment Emergent Events (SAFTEE) to assess safety and adverse effects. CBD peak plasma concentrations, time to reach peak plasma concentrations (tmax), and area under the curve (AUC) were measured.
RESULTS:
SAFTEE data were similar between groups without respiratory depression or cardiovascular complications during any test session. After low-dose CBD, tmax occurred at 3 and 1.5 hours in sessions 1 and 2, respectively. After high-dose CBD, tmax occurred at 3 and 4 hours in sessions 1 and 2, respectively. There were no significant differences in plasma CBD or cortisol (AUC P = NS) between sessions.
CONCLUSIONS:
Cannabidiol does not exacerbate adverse effects associated with intravenous fentanyl administration. Coadministration of CBD and opioids was safe and well tolerated. These data provide the foundation for future studies examining CBD as a potential treatment for opioid abuse.
PMID:

25748562
PMCID:
PMC4449284
DOI:
10.1097/ADM.0000000000000118
[Indexed for MEDLINE]
Free PMC Article

CBD: reduces chance of relapse, protects from Amphetamine

Psychopharmacology (Berl). 2015 Aug;232(16):3057-65. doi: 10.1007/s00213-015-3945-7. Epub 2015 May 6.

Cannabidiol effects in the prepulse inhibition disruption induced by amphetamine.

Pedrazzi JF1, Issy AC, Gomes FV, Guimarães FS, Del-Bel EA.
Author information

Abstract
RATIONALE:
The information processing appears to be deficient in schizophrenia. Prepulse inhibition (PPI), which measures the inhibition of a motor response by a weak sensory event, is considered particularly useful to understand the biology of information processing in schizophrenia patients. Drugs that facilitate dopaminergic neurotransmission such as amphetamine induce PPI disruption in human and rodents. Clinical and neurobiological findings suggest that the endocannabinoid system and cannabinoids may be implicated in the pathophysiology and treatment of schizophrenia. Cannabidiol (CBD), a non-psychotomimetic constituent of the Cannabis sativa plant, has also been reported to have potential as an antipsychotic.
OBJECTIVE:
Our aim was to investigate if CBD pretreatment was able to prevent PPI disruption induced by amphetamine. Since one possible mechanism of CBD action is the facilitation of endocannabinoid-mediated neurotransmission through anandamide, we tested the effects of an anandamide hydrolysis inhibitor (URB597) in the amphetamine-induced PPI disruption.
METHODS:
Male Swiss mice were treated with CBD systemic or intra-accumbens, or URB597 (systemic) prior to amphetamine and were exposed to PPI test.
RESULTS:
Amphetamine (10 mg/kg) disrupted PPI while CBD (15-60 mg/kg) or URB597 (0.1-1 mg/kg) administered alone had no effect. Pretreatment with CBD attenuated the amphetamine-disruptive effects on PPI test after systemic or intra-accumbens administration. Similar effects were also found with the inhibitor of anandamide hydrolysis.
CONCLUSION:
These results corroborate findings indicating that CBD induces antipsychotic-like effects. In addition, they pointed to the nucleus accumbens as a possible site of these effects. The increase of anandamide availability may be enrolled in the CBD effects.

PMID:
25943166
DOI:

10.1007/s00213-015-3945-7
[Indexed for MEDLINE]

CBD: alcohol

Psychopharmacology (Berl). 1979;66(1):45-50.

Interaction of cannabidiol and alcohol in humans.

Consroe P, Carlini EA, Zwicker AP, Lacerda LA.

Abstract

Six male and four female healthy volunteers were given oral placebo (glucose capsule and orange juice), cannabidiol (CBD 200 mg capsule and orange juice), alcohol (1 g/kg in orange juice and glucose capsule), and CBD (200 mg capsule) plus alcohol (1 g/kg in orange juice) in a double-blind, crossover, randomized design. Treatments were spaced one week apart. Parameters measured were a finger tap test (motor performance), cancellation and differential aptitude tests (psychomotor performance), a 1-min time production task, subjective effects (66 item adjective-pair semantic differential), and breathalyzer estimations of blood alcohol levels. Compared to placebo, alcohol and alcohol plus CBD, but not CBD alone, produced significant impairments of motor and psychomotor performances, overestimations of time production and subjective responses indicating an accurate self-perception of their intoxication and deficits. The combination of alcohol plus CBD resulted in significantly lower blood alcohol levels compared to alcohol given alone, however, there were few differences observed between the pharmacological effects of the two alcohol conditions. Thus, the inactivity of CBD, a major marijuana constituent, on motor and mental performance and effects also extends to its interaction with alcohol.

PMID:
120541
[Indexed for MEDLINE]

CBD: Serotonin / Fear / Reward

Neuropsychopharmacology. 2016 Nov;41(12):2839-2850. doi: 10.1038/npp.2016.93. Epub 2016 Jun 14.

Cannabidiol Modulates Fear Memory Formation Through Interactions with Serotonergic Transmission in the Mesolimbic System.

Norris C1,2, Loureiro M1,2, Kramar C1,2, Zunder J1,2, Renard J1,2, Rushlow W1,2,3, Laviolette SR1,2,3,4.
Author information

Abstract
Emerging evidence suggests that the largest phytochemical component of cannabis, cannabidiol (CBD), may possess pharmacotherapeutic properties in the treatment of neuropsychiatric disorders. CBD has been reported to functionally interact with both the mesolimbic dopamine (DA) and serotonergic (5-HT) receptor systems. However, the underlying mechanisms by which CBD may modulate emotional processing are not currently understood. Using a combination of in vivo electrophysiological recording and fear conditioning in rats, the present study aimed to characterize the behavioral, neuroanatomical, and pharmacological effects of CBD within the mesolimbic pathway, and its possible functional interactions with 5-HT and DAergic transmission. Using targeted microinfusions of CBD into the shell region of the mesolimbic nucleus accumbens (NASh), we report that intra-NASh CBD potently blocks the formation of conditioned freezing behaviors. These effects were challenged with DAergic, cannabinoid CB1 receptor, and serotonergic (5-HT1A) transmission blockade, but only 5-HT1A blockade restored associative conditioned freezing behaviors. In vivo intra-ventral tegmental area (VTA) electrophysiological recordings revealed that behaviorally effective doses of intra-NASh CBD elicited a predominant decrease in spontaneous DAergic neuronal frequency and bursting activity. These neuronal effects were reversed by simultaneous blockade of 5-HT1A receptor transmission. Finally, using a functional contralateral disconnection procedure, we demonstrated that the ability of intra-NASh CBD to block the formation of conditioned freezing behaviors was dependent on intra-VTA GABAergic transmission substrates. Our findings demonstrate a novel NAcVTA circuit responsible for the behavioral and neuronal effects of CBD within the mesolimbic system via functional interactions with serotonergic 5-HT1A receptor signaling.

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27296152
PMCID:
PMC5061893
DOI:
10.1038/npp.2016.93
[Indexed for MEDLINE]

J Neurosci. 2014 Sep 24;34(39):13096-109. doi: 10.1523/JNEUROSCI.1297-14.2014.

CBD: Positive emotional connections

Cannabinoid transmission in the prefrontal cortex bi-phasically controls emotional memory formation via functional interactions with the ventral tegmental area.

Draycott B1, Loureiro M1, Ahmad T1, Tan H1, Zunder J1, Laviolette SR2.
Author information

Abstract
Disturbances in cortical cannabinoid CB1 receptor signaling are well established correlates of various neuropsychiatric disorders, including depression and schizophrenia. Importantly, the ability of cannabinoid transmission to modulate emotional processing is functionally linked to interactions with subcortical DA systems. While considerable evidence demonstrates that CB1 receptor-mediated modulation of emotional processing and related behaviors follows a biphasic functional curve, little is known regarding how CB1 signaling within cortical networks may interact with subcortical DAergic systems involved in emotional behavior regulation. Using a combination of in vivo electrophysiological recordings and behavioral pharmacology in rats, we investigated the relationship between mPFC cannabinoid transmission, fear memory formation, and subcortical DA neuron activity patterns. We report that direct intra-mPFC CB1 activation biphasically modulates spontaneous, subcortical VTA DA neuron activity in a dose-dependent fashion; while lower doses of a CB1 receptor agonist, WIN 55,212-2, significantly increased spontaneous firing and bursting rates of VTA DA neurons, higher doses strongly inhibited spontaneous DA neuron activity. Remarkably, this same dose-related functional difference was observed with the regulation of fear-related emotional memory formation. Thus, lower levels of CB1 activation potentiated the emotional salience of normally subthreshold fear memory, whereas higher levels completely blocked fear memory acquisition. Furthermore, while the potentiation of subthreshold fear memory salience was blocked by DA receptor antagonism, CB1-mediated blunting of suprathreshold fear memory was rescued by intra-VTA administration of a GABAB receptor antagonist, demonstrating that reversal of GABAergic inhibitory mechanisms in the VTA can reverse the inhibitory influence of intra-PFC CB1 transmission on mesolimbic DA activity.

KEYWORDS:
cannabinoids; dopamine; fear memory; prefrontal cortex; ventral tegmental area
PMID:
25253856

DOI:
10.1523/JNEUROSCI.1297-14.2014
[Indexed for MEDLINE]

CBD: reduces fear memory

J Neurosci. 2011 Apr 6;31(14):5300-12. doi: 10.1523/JNEUROSCI.4718-10.2011.

Cannabinoid transmission in the basolateral amygdala modulates fear memory formation via functional inputs to the prelimbic cortex.

Tan H1, Lauzon NM, Bishop SF, Chi N, Bechard M, Laviolette SR.
Author information

Abstract
The cannabinoid CB1 receptor system is critically involved in the control of associative fear memory formation within the amygdala-prefrontal cortical pathway. The CB1 receptor is found in high concentrations in brain structures that are critical for emotional processing, including the basolateral amygdala (BLA) and the prelimbic division (PLC) of the medial prefrontal cortex (mPFC). However, the precise role of CB1 receptor transmission within the BLA during the processing of fear memory is not fully understood. We examined the potential role of BLA CB1 receptor transmission during an olfactory fear-conditioning procedure in rats by pharmacologically modulating CB1 cannabinoid transmission directly within the BLA. We report that blockade of BLA CB1 receptor transmission prevents the acquisition of associative fear memory, while having no effect on the recall or consolidation of these memories. In contrast, intra-BLA activation of CB1 receptor transmission or blockade of endocannabinoid reuptake strongly potentiated the emotional salience of normally subthreshold fear-conditioning stimuli. In addition, pharmacological inactivation of the mPFC before intra-BLA CB1 activation blocked CB1-receptor-mediated potentiation of fear memory formation. In vivo single-unit electrophysiological recordings within the PLC revealed that modulation of BLA CB1 receptor transmission strongly influences neuronal activity within subpopulations of PLC neurons, with blockade of intra-BLA CB1 receptor transmission inhibiting spontaneous PLC neuronal activity and activation of CB1 receptors producing robust activation, in terms of neuronal firing frequency and bursting activity. Thus, cannabinoid transmission within the BLA strongly modulates the processing of associative fear memory via functional interactions with PLC neuronal populations.

PMID:
21471365
DOI:
10.1523/JNEUROSCI.4718-10.2011
[Indexed for MEDLINE]
Free full text

CBD: control opiate reward

J Neurosci. 2013 Sep 25;33(39):15642-51. doi: 10.1523/JNEUROSCI.1686-13.2013.

Cannabinoid transmission in the prelimbic cortex bidirectionally controls opiate reward and aversion signaling through dissociable kappa versus μ-opiate receptor dependent mechanisms.

Ahmad T1, Lauzon NM, de Jaeger X, Laviolette SR.
Author information

Abstract
Cannabinoid, dopamine (DA), and opiate receptor pathways play integrative roles in emotional learning, associative memory, and sensory perception. Modulation of cannabinoid CB1 receptor transmission within the medial prefrontal cortex (mPFC) regulates the emotional valence of both rewarding and aversive experiences. Furthermore, CB1 receptor substrates functionally interact with opiate-related motivational processing circuits, particularly in the context of reward-related learning and memory. Considerable evidence demonstrates functional interactions between CB1 and DA signaling pathways during the processing of motivationally salient information. However, the role of mPFC CB1 receptor transmission in the modulation of behavioral opiate-reward processing is not currently known. Using an unbiased conditioned place preference paradigm with rats, we examined the role of intra-mPFC CB1 transmission during opiate reward learning. We report that activation or inhibition of CB1 transmission within the prelimbic cortical (PLC) division of the mPFC bidirectionally regulates the motivational valence of opiates; whereas CB1 activation switched morphine reward signaling into an aversive stimulus, blockade of CB1 transmission potentiated the rewarding properties of normally sub-reward threshold conditioning doses of morphine. Both of these effects were dependent upon DA transmission as systemic blockade of DAergic transmission prevented CB1-dependent modulation of morphine reward and aversion behaviors. We further report that CB1-mediated intra-PLC opiate motivational signaling is mediated through a μ-opiate receptor-dependent reward pathway, or a κ-opiate receptor-dependent aversion pathway, directly within the ventral tegmental area. Our results provide evidence for a novel CB1-mediated motivational valence switching mechanism within the PLC, controlling dissociable subcortical reward and aversion pathways.

PMID:
24068830
DOI:
10.1523/JNEUROSCI.1686-13.2013
[Indexed for MEDLINE]
Free full text

CBD: dopamine, reward memory formation, social interaction.

Neuropsychopharmacology. 2015 May;40(6):1436-47. doi: 10.1038/npp.2014.329. Epub 2014 Dec 16.

Hippocampal cannabinoid transmission modulates dopamine neuron activity: impact on rewarding memory formation and social interaction.

Loureiro M1, Renard J1, Zunder J1, Laviolette SR2.
Author information

Abstract
Disturbances in cannabinoid type 1 receptor (CB1R) signaling have been linked to emotional and cognitive deficits characterizing neuropsychiatric disorders, including schizophrenia. Thus, there is growing interest in characterizing the relationship between cannabinoid transmission, emotional processing, and dopamine (DA)-dependent behavioral deficits. The CB1R is highly expressed in the mammalian nervous system, particularly in the hippocampus. Activation of the ventral hippocampal subregion (vHipp) is known to increase both the activity of DAergic neurons located in the ventral tegmental area (VTA) and DA levels in reward-related brain regions, particularly the nucleus accumbens (NAc). However, the possible functional relationship between hippocampal CB1R transmission and VTA DA neuronal activity is not currently understood. In this study, using in vivo neuronal recordings in rats, we demonstrate that activation of CB1R in the vHipp strongly increases VTA DA neuronal firing and bursting activity, while simultaneously decreasing the activity of VTA non-DA neurons. Furthermore, using a conditioned place preference procedure and a social interaction test, we report that intra-vHipp CB1R activation potentiates the reward salience of normally sub-threshold conditioning doses of opiates and induces deficits in natural sociability and social recognition behaviors. Finally, these behavioral effects were prevented by directly blocking NAc DAergic transmission. Collectively, these findings identify hippocampal CB1R transmission as a critical modulator of the mesolimbic DA pathway and in the processing of reward and social-related behavioral phenomena.

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25510937
PMCID:
PMC4397402
DOI:
10.1038/npp.2014.329
[Indexed for MEDLINE]
Free PMC Article

CBD: reward and aversion = good mood.

Biol Psychiatry. 2016 Aug 1;80(3):216-25. doi: 10.1016/j.biopsych.2015.10.016. Epub 2015 Oct 31.

Cannabinoid Transmission in the Hippocampus Activates Nucleus Accumbens Neurons and Modulates Reward and Aversion-Related Emotional Salience.

Loureiro M1, Kramar C2, Renard J2, Rosen LG2, Laviolette SR3.
Author information

Abstract
BACKGROUND:
Cannabinoid receptor transmission strongly influences emotional processing, and disturbances in cannabinoid signaling are associated with various neuropsychiatric disorders. The mammalian ventral hippocampus (vHipp) is a critical neural region controlling mesolimbic activity via glutamatergic projections to the nucleus accumbens. Furthermore, vHipp abnormalities are linked to schizophrenia-related psychopathology. Nevertheless, the mechanisms by which intra-vHipp cannabinoid signaling may modulate mesolimbic activity states and emotional processing are not currently understood.
METHODS:
Using an integrative combination of in vivo electrophysiological recordings and behavioral pharmacologic assays in rats, we tested whether activation of cannabinoid type 1 receptors (CB1R) in the vHipp may modulate neuronal activity in the shell subregion of the nucleus accumbens (NASh). We next examined how vHipp CB1R signaling may control the salience of rewarding or aversive emotional memory formation and social interaction/recognition behaviors via intra-NASh glutamatergic transmission.
RESULTS:
We demonstrate for the first time that vHipp CB1R transmission can potently modulate NASh neuronal activity and can differentially control the formation of context-dependent and context-independent forms of rewarding or aversion-related emotional associative memories. In

addition, we found that activation of vHipp CB1R transmission strongly disrupts normal social behavior and cognition. Finally, we report that these behavioral effects are dependent upon intra-NASh alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid/N-methyl-D-aspartate receptor transmission.
CONCLUSIONS:
Together, these findings demonstrate a critical role for hippocampal cannabinoid signaling in the modulation of mesolimbic neuronal activity states and suggest that dysregulation of CB1R transmission in the vHipp→NASh circuit may underlie hippocampal-mediated affective and social behavioral disturbances present in neuropsychiatric disorders.

KEYWORDS:
Addiction; CB(1) receptor; Glutamate; Morphine; Schizophrenia; Ventral hippocampus
PMID:
26681496
DOI:
10.1016/j.biopsych.2015.10.016
[Indexed for MEDLINE]

CBD: bidirectional reward/aversion signaling

Addict Biol. 2017 Sep;22(5):1218-1231. doi: 10.1111/adb.12406. Epub 2016 May 27.

Bi-directional cannabinoid signalling in the basolateral amygdala controls rewarding and aversive emotional processing via functional regulation of the nucleus accumbens.

Ahmad T1,2, Sun N1,2, Lyons D1,2, Laviolette SR1,2,3,4.
Author information

Abstract

Functional connections between the basolateral amygdala (BLA) and nucleus accumbens (NAc) are involved critically in opiate-reward processing. In the BLA, inhibitory GABAergic substrates are inhibited by cannabinoid CB1 receptor (CB1R) activation and can modulate BLA projections to various limbic regions, including the NAc. However, the potential role of CB1R transmission in the regulation of opiate-related memory formation via the BLA→NAc circuit is not understood. Using an unbiased conditioned place preference paradigm in rats, we examined the effects of intra-BLA CB1R modulation by either direct pharmacological activation or blockade of CB1R transmission. We report that intra-BLA CB1R activation switches normally rewarding effects of morphine into strongly aversive effects. In contrast, CB1R blockade strongly potentiates normally subreward threshold effects of morphine. Next, using targeted microinfusions of an NMDA receptor antagonist to either the core or shell (NASh) subdivisions of the NAc, we found that selective blockade of NMDA transmission in the NA shell, but not core, prevented both intra-BLA CB1 blockade-mediated opiate reward potentiation and CB1 activation-mediated aversion effects. Finally, using multi-unit, in vivo electrophysiological recordings in the NASh, we report that the ability of intra-BLA CB1R modulation to control opiate reward salience and motivational valence is associated with distinct reward or aversion neuronal activity patterns and bi-directional regulation of intra-NASh fast-spiking interneurons versus medium spiny neurons. These findings identify a unique mechanism whereby bi-directional BLA CB1R transmission can regulate opiate-related motivational processing and control affective states through functional modulation of mesolimbic neuronal activity.

KEYWORDS:
Amygdala; cannabinoid; dopamine; nucleus accumbens; opiates
PMID:
27230434
DOI:
10.1111/adb.12406
[Indexed for MEDLINE]

CBD: social activity, memory

Psychopharmacology (Berl). 2014 Aug;231(15):3009-17. doi: 10.1007/s00213-014-3478-5. Epub 2014 Mar 1.

Chronic cannabidiol treatment improves social and object recognition in double transgenic APPswe/PS1ΔE9 mice.

Cheng D1, Low JK, Logge W, Garner B, Karl T.

Abstract

RATIONALE:

Patients suffering from Alzheimer's disease (AD) exhibit a decline in cognitive abilities including an inability to recognise familiar faces. Hallmark pathological changes in AD include the aggregation of amyloid-β (Aβ), tau protein hyperphosphorylation as well as pronounced neurodegeneration, neuroinflammation, neurotoxicity and oxidative damage.

OBJECTIVES:

The non-psychoactive phytocannabinoid cannabidiol (CBD) exerts neuroprotective, anti-oxidant and anti-inflammatory effects and promotes neurogenesis. CBD also reverses Aβ-induced spatial memory deficits in rodents.

MATERIALS AND METHODS:

Thus we determined the therapeutic-like effects of chronic CBD treatment (20 mg/kg, daily intraperitoneal injections for 3 weeks) on the APPswe/PS1ΔE9 (APPxPS1) transgenic mouse model for AD in a number of cognitive tests, including the social preference test, the novel object recognition task and the fear conditioning paradigm. We also analysed the impact of CBD on anxiety behaviours in the elevated plus maze.

RESULTS:

Vehicle-treated APPxPS1 mice demonstrated impairments in social recognition and novel object recognition compared to wild type-like mice. Chronic CBD treatment reversed these cognitive deficits in APPxPS1 mice without affecting anxiety-related behaviours.

CONCLUSIONS:

This is the first study to investigate the effect of chronic CBD treatment on cognition in an AD transgenic mouse model. Our findings suggest that CBD may have therapeutic potential for specific cognitive impairments associated with AD.

PMID:

24577515

DOI:
10.1007/s00213-014-3478-5

CBD: fear extinction

Front Pharmacol. 2016 Dec 16;7:493. doi: 10.3389/fphar.2016.00493. eCollection 2016.

Bidirectional Effects of Cannabidiol on Contextual Fear Memory Extinction.

Song C1, Stevenson CW2, Guimaraes FS3, Lee JL1.
Author information

Abstract
Cannabidiol (CBD) has been established to have both acute and long-lasting effects to reduce fear memory expression. The long-lasting impact might be mediated by an enhancement of memory extinction or an impairment of memory reconsolidation. Here, we directly compared the effects of i.p. injections of cannabidiol (10 mg/kg) with those of the NMDA receptor antagonist MK-801 (0.1 mg/kg) and partial agonist D-cycloserine (DCS; 15 mg/kg) in order to determine the mnemonic basis of long-term fear reduction. We showed that under conditions of strong fear conditioning, CBD reduced contextual fear memory expression both acutely during the extinction session as well as later at a fear retention test. The latter test reduction was replicated by DCS, but MK-801 instead elevated test freezing. In contrast, when initial conditioning was weaker, CBD and MK-801 had similar effects to increase freezing at the fear retention test relative to vehicle controls, whereas DCS had no observable impact. This pattern of results is consistent with CBD enhancing contextual fear memory extinction when the initial conditioning is strong, but impairing extinction when conditioning is weak. This bidirectional effect of CBD may be related to stress levels induced by conditioning and evoked at retrieval during extinction, rather than the strength of the memory per se.

KEYWORDS:
cannabinoid; contextual; extinction; fear; memory
PMID:
28018227
PMCID:
PMC5159417
DOI:
10.3389/fphar.2016.00493

CBD: learned fear and anxiety

Front Pharmacol. 2016 Nov 24;7:454. eCollection 2016.

Cannabidiol Regulation of Learned Fear: Implications for Treating Anxiety-Related Disorders.

Jurkus R1, Day HL2, Guimarães FS3, Lee JL4, Bertoglio LJ5, Stevenson CW2.
Author information

Abstract
Anxiety and trauma-related disorders are psychiatric diseases with a lifetime prevalence of up to 25%. Phobias and post-traumatic stress disorder (PTSD) are characterized by abnormal and persistent memories of fear-related contexts and cues. The effects of psychological treatments such as exposure therapy are often only temporary and medications can be ineffective and have adverse side effects. Growing evidence from human and animal studies indicates that cannabidiol, the main non-psychotomimetic phytocannabinoid present in Cannabis sativa, alleviates anxiety in paradigms assessing innate fear. More recently, the effects of cannabidiol on learned fear have been investigated in preclinical studies with translational relevance for phobias and PTSD. Here we review the findings from these studies, with an emphasis on cannabidiol regulation of contextual fear. The evidence indicates that cannabidiol reduces learned fear in different ways: (1) cannabidiol decreases fear expression acutely, (2) cannabidiol disrupts memory reconsolidation, leading to sustained fear attenuation upon memory retrieval, and (3) cannabidiol enhances extinction, the psychological process by which exposure therapy inhibits learned fear. We also present novel data on cannabidiol regulation of learned fear related to explicit cues, which indicates that auditory fear expression is also reduced acutely by cannabidiol. We conclude by outlining future directions for research to elucidate the neural circuit, psychological, cellular, and molecular mechanisms underlying the regulation of fear memory processing by cannabidiol. This line of investigation may lead to the development of cannabidiol as a novel therapeutic approach for treating anxiety and trauma-related disorders such as phobias and PTSD in the future.

KEYWORDS:
cannabidiol; extinction; fear conditioning; reconsolidation
PMID:
27932983
PMCID:
PMC5121237
DOI:
10.3389/fphar.2016.00454

CBD: fear extinction

Psychopharmacology (Berl). 2013 Apr;226(4):781-92. doi: 10.1007/s00213-012-2955-y. Epub 2013 Jan 10.

Cannabidiol enhances consolidation of explicit fear extinction in humans.

Das RK1, Kamboj SK, Ramadas M, Yogan K, Gupta V, Redman E, Curran HV, Morgan CJ.
Author information

Abstract
RATIONALE:
Whilst Cannabidiol (CBD), a non-psychotomimetic cannabinoid, has been shown to enhance extinction learning in rats, its effects on fear memory in humans have not previously been studied.
OBJECTIVES:
We employed a Pavlovian fear-conditioning paradigm in order to assess the effects of CBD on extinction and consolidation.
METHOD:
Forty-eight participants were conditioned to a coloured box (CS) with electric shocks (UCS) in one context and were extinguished in a second context. Participants received 32 mg of CBD either following before or after extinction in a double-blind, placebo-controlled design. At recall, 48 h later, participants were exposed to CSs and conditioning contexts before (recall) and after (reinstatement) exposure to the UCS. Skin conductance and shock expectancy measures of conditioned responding were recorded throughout.
RESULTS:
Successful conditioning, extinction and recall were found in all three treatment groups. CBD given post-extinction enhanced consolidation of extinction learning as assessed by shock expectancy. CBD administered at either time produced trend level reduction in reinstatement of autonomic contextual responding. No acute effects of CBD were found on extinction.
CONCLUSIONS:
These findings provide the first evidence that CBD can enhance consolidation of extinction learning in humans and suggest that CBD may have potential as an adjunct to extinction-based therapies for anxiety disorders.

PMID:
23307069
DOI:
10.1007/s00213-012-2955-y

CBD: protects memory in rehab

Subst Abuse Rehabil. 2013 Jan 23;4:11-27. doi: 10.2147/SAR.S25869. eCollection 2013.

The effect of cannabis use on memory function: an update.

Schoeler T1, Bhattacharyya S1.
Author information

Abstract
Investigating the effects of cannabis use on memory function appears challenging. While early observational investigations aimed to elucidate the longer-term effects of cannabis use on memory function in humans, findings remained equivocal and pointed to a pattern of interacting factors impacting on the relationship between cannabis use and memory function, rather than a simple direct effect of cannabis. Only recently, a clearer picture of the chronic and acute effects of cannabis use on memory function has emerged once studies have controlled for potential confounding factors and started to investigate the acute effects of delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), the main ingredients in the extract of the cannabis plant in pharmacological challenge experiments. Relatively consistent findings have been reported regarding the acute impairments induced by a single dose of Δ9-THC on verbal and working memory. It is unclear whether they may persist beyond the intoxication state. In the long-term, these impairments seem particularly likely to manifest and may also persist following abstinence if regular and heavy use of cannabis strains high in Δ9-THC is started at an early age. Although still at an early stage, studies that employed advanced neuroimaging techniques have started to model the neural underpinnings of the effects of cannabis use and implicate a network of functional and morphological alterations that may moderate the effects of cannabis on memory function. Future experimental and epidemiological studies that take into consideration individual differences, particularly previous cannabis history and demographic characteristics, but also the precise mixture of the ingredients of the consumed cannabis are necessary to clarify the magnitude and the mechanisms by which cannabis-induced memory impairments occur and to elucidate underlying neurobiological mechanisms.

KEYWORDS:
CBD; THC; cannabis; fMRI; memory; neuroimaging

CBD: positive emotions and memories in anxiety and addiction

Br J Pharmacol. 2017 Oct;174(19):3242-3256. doi: 10.1111/bph.13724. Epub 2017 Mar 9.

Cannabidiol regulation of emotion and emotional memory processing: relevance for treating anxiety-related and substance abuse disorders.

Lee JLC1, Bertoglio LJ2, Guimarães FS3, Stevenson CW4.
Author information

Abstract
Learning to associate cues or contexts with potential threats or rewards is adaptive and enhances survival. Both aversive and appetitive memories are therefore powerful drivers of behaviour, but the inappropriate expression of conditioned responding to fear- and drug-related stimuli can develop into anxiety-related and substance abuse disorders respectively. These disorders are associated with abnormally persistent emotional memories and inadequate treatment, often leading to symptom relapse. Studies show that cannabidiol, the main non-psychotomimetic phytocannabinoid found in Cannabis sativa, reduces anxiety via 5-HT1A and (indirect) cannabinoid receptor activation in paradigms assessing innate responses to threat. There is also accumulating evidence from animal studies investigating the effects of cannabidiol on fear memory processing indicating that it reduces learned fear in paradigms that are translationally relevant to phobias and post-traumatic stress disorder. Cannabidiol does so by reducing fear expression acutely and by disrupting fear memory reconsolidation and enhancing fear extinction, both of which can result in a lasting reduction of learned fear. Recent studies have also begun to elucidate the effects of cannabidiol on drug memory expression using paradigms with translational relevance to addiction. The findings suggest that cannabidiol reduces the expression of drug memories acutely and by disrupting their reconsolidation. Here, we review the literature demonstrating the anxiolytic effects of cannabidiol before focusing on studies investigating its effects on various fear and drug memory processes. Understanding how cannabidiol regulates emotion and emotional memory processing may eventually lead to its use as a treatment for anxiety-related and substance abuse disorders. Linked Articles This article is part of a themed section on Pharmacology of Cognition: a Panacea for Neuropsychiatric Disease? To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.19/issuetoc.

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28268256
PMCID:
PMC5595771
DOI:

10.1111/bph.13724
[Indexed for MEDLINE]
Free PMC Article

CBD: fear extinction

Eur Neuropsychopharmacol. 2008 Dec;18(12):849-59. doi: 10.1016/j.euroneuro.2008.07.001. Epub 2008 Aug 15.

Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats.

Bitencourt RM1, Pamplona FA, Takahashi RN.
Author information

Abstract
The present study investigated the central effects of the eCB uptake/metabolism inhibitor AM404 and the phytocannabinoid cannabidiol (CBD) on the extinction of contextual fear memories in rats. Rats were conditioned and 24 h later subjected to three consecutive 9-min non-reinforced exposures to the conditioning context (extinction sessions, 24 h intervals). AM404 or CBD was injected i.c.v. 5 min before each extinction session and a 3-min drug-free test of contextual memory was performed 24 h after the last extinction session. AM404 (1.0 microg/microl, i.c.v.) and CBD (2.0 microg/microl, i.c.v.) facilitated extinction of contextual fear memory, with persistent effects. These responses were antagonized by the CB1-selective antagonist SR141716A (0.2 mg/kg, i.p.), but not by the TRPV1-selective antagonist capsazepine (5.0 microg/microl, i.c.v.). The effect of the anxiolytic drug Diazepam (DZP) on the extinction of contextual fear memory was also investigated. In contrast with the CBD and AM404 results, DZP induced a general reduction in the expression of conditioned freezing. Both AM404 and CBD induced anti-anxiogenic effect in the fear-potentiated plus-maze test, whereas DZP was anxiolytic in conditioned and unconditioned rats. In conclusion, CBD, a non-psychoactive phytocannabinoid could be an interesting pharmacological approach to reduce the anxiogenic effects of stress and promote the extinction of fear memories.

PMID:
18706790
DOI:
10.1016/j.euroneuro.2008.07.001

CBD: morphine

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]

CBD: morphine

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

Opiate Addiction

Blockade of endocannabinoid hydrolytic enzymes attenuates precipitated opioid withdrawal symptoms in mice.

University of VA, 2011: https://www.ncbi.nlm.nih.gov/pubmed/21719468

ABSTRACT: Δ(9)-Tetrahydrocannbinol (THC), the primary active constituent of Cannabis sativa, has long been known to reduce opioid withdrawal symptoms. Although THC produces most of its pharmacological actions through the activation of CB(1) and CB(2) cannabinoid receptors, the role these receptors play in reducing the variety of opioid withdrawal symptoms remains unknown. The endogenous cannabinoids, N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonylglycerol (2-AG), activate both cannabinoid receptors but are rapidly metabolized by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. The objective of this study was to test whether increasing AEA or 2-AG, via inhibition of their respective hydrolytic enzymes, reduces naloxone-precipitated morphine withdrawal symptoms in in vivo and in vitro models of opioid dependence. Morphine-dependent mice challenged with naloxone reliably displayed a profound withdrawal syndrome, consisting of jumping, paw tremors, diarrhea, and weight loss. THC and the MAGL inhibitor 4-nitrophenyl 4-(dibenzo[d][1,3]dioxol-5-yl(hydroxy)methyl)piperidine-1-carboxylate (JZL184) dose dependently reduced the intensity of most measures through the activation of CB(1) receptors. JZL184 also attenuated spontaneous withdrawal signs in morphine-dependent mice. The FAAH inhibitor N-(pyridin-3-yl)-4-(3-(5-(trifluoromethyl)pyridin-2-yloxy)benzyl)-piperdine-1-carboxamide (PF-3845) reduced the intensity of naloxone-precipitated jumps and paw flutters through the activation of CB(1) receptors but did not ameliorate incidence of diarrhea or weight loss. In the final series of experiments, we investigated whether JZL184 or PF-3845 would attenuate naloxone-precipitated contractions in morphine-dependent ilea. Both enzyme inhibitors attenuated the intensity of naloxone-induced contractions, although this model does not account mechanistically for the autonomic withdrawal responses (i.e., diarrhea) observed in vivo. These results indicate that endocannabinoid catabolic enzymes are promising targets to treat opioid dependence.

400mg & 800mg Oral CBD Oil Bioavailability when combined with Fentanyl

Plasma CBD Concentrations (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4449284/)

Plasma CBD concentrations were measured at baseline and at selected time points according to the protocol outlined in Figure 1. Group 1 (placebo) measurements served as the negative control. In Group 2 (400mg CBD), time to peak plasma concentrations (t_{max}) occurred at 3h (mean C_{max} 181.2±39.8µg/L) and 1.5h (C_{max} 114.2±19.5µg/L)in Sessions 1 (0.5 mcg/kg fentanyl) and 2 (1.0 mcg/kg fentanyl), respectively (Fig. 2A). In Group 3 (800mg CBD), t_{max} occurred at 3h (mean C_{max} 221.1±35.6µg/L) and 4h (mean C_{max} 157.1±49.0µg/L) in Sessions 1 and 2, respectively (Fig. 2B). In Group 2, AUC (mcg*hr/dL) for Sessions 1 and 2 were 704±283 and 482±314, while Group 3 with the highest CBD dose tested had AUCs of 867± 304 and 722±443, respectively ($F[2,14] = 55.34$; $p < 0.0001$).

CBD - Heroin

Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances.

J Neurosci. 2009 Nov 25;29(47):14764-9. doi: 10.1523/JNEUROSCI.4291-09.2009. **Author information**

Abstract

There remains debate regarding the impact of cannabis on neuropsychiatric disorders. Here, we examined the effects of cannabidiol (CBD), a non psychoactive constituent of cannabis, on heroin self-administration and drug-seeking behavior using an experimental rat model. CBD (5-20 mg/kg) did not alter stable intake of heroin self-administration, extinction behavior, or drug seeking induced by a heroin prime injection. Instead, it specifically attenuated heroin-seeking behavior reinstated by exposure to a conditioned stimulus cue. CBD had a protracted effect with significance evident after 24 h and even 2 weeks after administration. The behavioral effects were paralleled by neurobiological alterations in the glutamatergic and endocannabinoid systems. Discrete disturbances of AMPA GluR1 and cannabinoid type-1 receptor expression observed in the nucleus accumbens associated with stimulus cue-induced heroin seeking were normalized by CBD treatment. The findings highlight the unique contributions of distinct cannabis constituents to addiction vulnerability and suggest that CBD may be a potential treatment for heroin craving and relapse.

CBD: Addiction

Addict Biol. 2017 May;22(3):742-751. doi: 10.1111/adb.12366. Epub 2016 Feb 1.

Cannabidiol disrupts the reconsolidation of contextual drug-associated memories in Wistar rats.

de Carvalho CR1, Takahashi RN1.
Author information

Abstract
In addicts, craving and relapse are frequently induced by the recall of memories related to a drug experience. Several studies have demonstrated that drug-related memories are reactivated after exposure to environmental cues and may undergo reconsolidation, a process that can strengthen memories. Thus, reactivation of mnemonic traces provides an opportunity for disrupting memories that contribute to the pathological cycle of addiction. Here we used drug-induced conditioned place preference (CPP) to investigate whether cannabidiol (CBD), a phytocannabinoid, given just after reactivation sessions, would affect reconsolidation of drug-reward memory, reinstatement of morphine-CPP, or conditioned place aversion precipitated by naltrexone in Wistar rats. We found that CBD impaired the reconsolidation of preference for the environment previously paired with both morphine and cocaine. This disruption seems to be persistent, as the preference did not return after further reinstatement induced by priming drug and stress reinstatement. Moreover, in an established morphine-CPP, an injection of CBD after the exposure to a conditioning session led to a significant reduction of both morphine-CPP and subsequent conditioned place aversion precipitated by naltrexone in the same context. Thus, established memories induced by a drug of abuse can be blocked after reactivation of the drug experience. Taken together, these results provide evidence for the disruptive effect of CBD on reconsolidation of contextual drug-related memories and highlight its therapeutic potential to attenuate contextual memories associated with drugs of abuse and consequently to reduce the risk of relapse.

KEYWORDS:
cannabidiol; conditioned place preference; memory reconsolidation

CBD: Memory

Subst Abuse Rehabil. 2013 Jan 23;4:11-27. doi: 10.2147/SAR.S25869. eCollection 2013.

The effect of cannabis use on memory function: an update.

Schoeler T1, Bhattacharyya S1.
Author information

Abstract
Investigating the effects of cannabis use on memory function appears challenging. While early observational investigations aimed to elucidate the longer-term effects of cannabis use on memory function in humans, findings remained equivocal and pointed to a pattern of interacting factors impacting on the relationship between cannabis use and memory function, rather than a simple direct effect of cannabis. Only recently, a clearer picture of the chronic and acute effects of cannabis use on memory function has emerged once studies have controlled for potential confounding factors and started to investigate the acute effects of delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD), the main ingredients in the extract of the cannabis plant in pharmacological challenge experiments. Relatively consistent findings have been reported regarding the acute impairments induced by a single dose of Δ9-THC on verbal and working memory. It is unclear whether they may persist beyond the intoxication state. In the long-term, these impairments seem particularly likely to manifest and may also persist following abstinence if regular and heavy use of cannabis strains high in Δ9-THC is started at an early age. Although still at an early stage, studies that employed advanced neuroimaging techniques have started to model the neural underpinnings of the effects of cannabis use and implicate a network of functional and morphological alterations that may moderate the effects of cannabis on memory function. Future experimental and epidemiological studies that take into consideration individual differences, particularly previous cannabis history and demographic characteristics, but also the precise mixture of the ingredients of the consumed cannabis are necessary to clarify the magnitude and the mechanisms by which cannabis-induced memory impairments occur and to elucidate underlying neurobiological mechanisms.

KEYWORDS:
CBD; THC; cannabis; fMRI; memory; neuroimaging

CBD: Amphetamines

J Neurosci. 2016 May 4;36(18):5160-9. doi: 10.1523/JNEUROSCI.3387-15.2016.

Cannabidiol Counteracts Amphetamine-Induced Neuronal and Behavioral Sensitization of the Mesolimbic Dopamine Pathway through a Novel mTOR/p70S6 Kinase Signaling Pathway.

Renard J1, Loureiro M1, Rosen LG1, Zunder J1, de Oliveira C2, Schmid S2, Rushlow WJ3, Laviolette SR4.
Author information

Abstract
Schizophrenia-related psychosis is associated with disturbances in mesolimbic dopamine (DA) transmission, characterized by hyperdopaminergic activity in the mesolimbic pathway. Currently, the only clinically effective treatment for schizophrenia involves the use of antipsychotic medications that block DA receptor transmission. However, these medications produce serious side effects leading to poor compliance and treatment outcomes. Emerging evidence points to the involvement of a specific phytochemical component of marijuana called cannabidiol (CBD), which possesses promising therapeutic properties for the treatment of schizophrenia-related psychoses. However, the neuronal and molecular mechanisms through which CBD may exert these effects are entirely unknown. We used amphetamine (AMPH)-induced sensitization and sensorimotor gating in rats, two preclinical procedures relevant to schizophrenia-related psychopathology, combined with in vivo single-unit neuronal electrophysiology recordings in the ventral tegmental area, and molecular analyses to characterize the actions of CBD directly in the nucleus accumbens shell (NASh), a brain region that is the current target of most effective antipsychotics. We demonstrate that Intra-NASh CBD attenuates AMPH-induced sensitization, both in terms of DAergic neuronal activity measured in the ventral tegmental area and psychotomimetic behavioral analyses. We further report that CBD controls downstream phosphorylation of the mTOR/p70S6 kinase signaling pathways directly within the NASh. Our findings demonstrate a novel mechanism for the putative antipsychotic-like properties of CBD in the mesolimbic circuitry. We identify the molecular signaling pathways through which CBD may functionally reduce schizophrenia-like neuropsychopathology.
SIGNIFICANCE STATEMENT:
The cannabis-derived phytochemical, cannabidiol (CBD), has been shown to have pharmacotherapeutic efficacy for the treatment of schizophrenia. However, the mechanisms by which CBD may produce antipsychotic effects are entirely unknown. Using preclinical behavioral procedures combined with molecular analyses and in vivo neuronal electrophysiology, our findings identify a functional role for the nucleus accumbens as a critical brain region whereby CBD can produce effects similar to antipsychotic medications by triggering molecular signaling

pathways associated with the effects of classic antipsychotic medications. Specifically, we report that CBD can attenuate both behavioral and dopaminergic neuronal correlates of mesolimbic dopaminergic sensitization, via a direct interaction with mTOR/p70S6 kinase signaling within the mesolimbic pathway.

KEYWORDS:
cannabidiol; dopamine; mesolimbic system; nucleus accumbens; schizophrenia; ventral tegmental area
PMID:
27147666
PMCID:
PMC4854973
DOI:
10.1523/JNEUROSCI.3387-15.2016
[Indexed for MEDLINE]
Free PMC Article

CBD: Amphetamines

Psychopharmacology (Berl). 2015 Aug;232(16):3057-65. doi: 10.1007/s00213-015-3945-7. Epub 2015 May 6.

Cannabidiol effects in the prepulse inhibition disruption induced by amphetamine.

Pedrazzi JF1, Issy AC, Gomes FV, Guimarães FS, Del-Bel EA.
Author information

Abstract
RATIONALE:
The information processing appears to be deficient in schizophrenia. Prepulse inhibition (PPI), which measures the inhibition of a motor response by a weak sensory event, is considered particularly useful to understand the biology of information processing in schizophrenia patients. Drugs that facilitate dopaminergic neurotransmission such as amphetamine induce PPI disruption in human and rodents. Clinical and neurobiological findings suggest that the endocannabinoid system and cannabinoids may be implicated in the pathophysiology and treatment of schizophrenia. Cannabidiol (CBD), a non-psychotomimetic constituent of the Cannabis sativa plant, has also been reported to have potential as an antipsychotic.
OBJECTIVE:
Our aim was to investigate if CBD pretreatment was able to prevent PPI disruption induced by amphetamine. Since one possible mechanism of CBD action is the facilitation of endocannabinoid-mediated neurotransmission through anandamide, we tested the effects of an anandamide hydrolysis inhibitor (URB597) in the amphetamine-induced PPI disruption.
METHODS:
Male Swiss mice were treated with CBD systemic or intra-accumbens, or URB597 (systemic) prior to amphetamine and were exposed to PPI test.
RESULTS:
Amphetamine (10 mg/kg) disrupted PPI while CBD (15-60 mg/kg) or URB597 (0.1-1 mg/kg) administered alone had no effect. Pretreatment with CBD attenuated the amphetamine-disruptive effects on PPI test after systemic or intra-accumbens administration. Similar effects were also found with the inhibitor of anandamide hydrolysis.
CONCLUSION:
These results corroborate findings indicating that CBD induces antipsychotic-like effects. In addition, they pointed to the nucleus accumbens as a possible site of these effects. The increase of anandamide availability may be enrolled in the CBD effects.

PMID:
25943166
DOI:
10.1007/s00213-015-3945-7
[Indexed for MEDLINE]

CBD: Opiate Addiction

Neurotherapeutics. 2015 Oct;12(4):807-15. doi: 10.1007/s13311-015-0373-7.

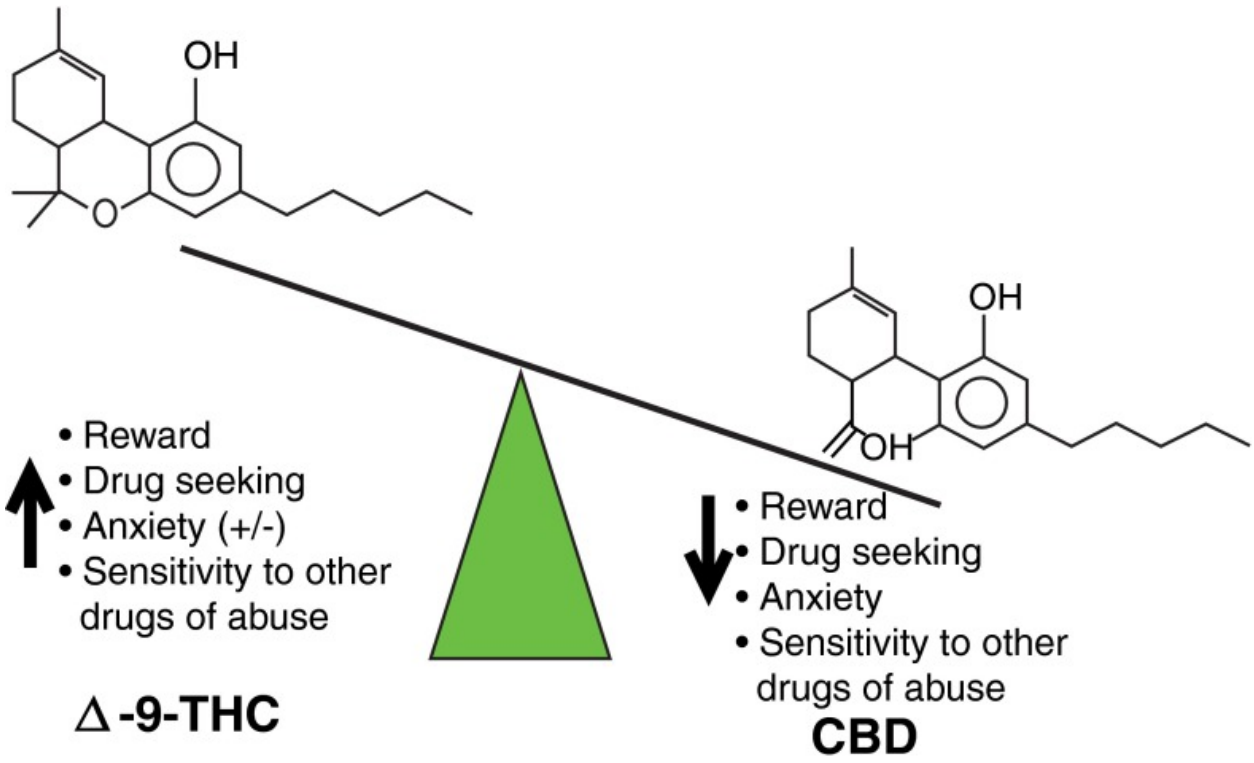
Early Phase in the Development of Cannabidiol as a Treatment for Addiction: Opioid Relapse Takes Initial Center Stage.

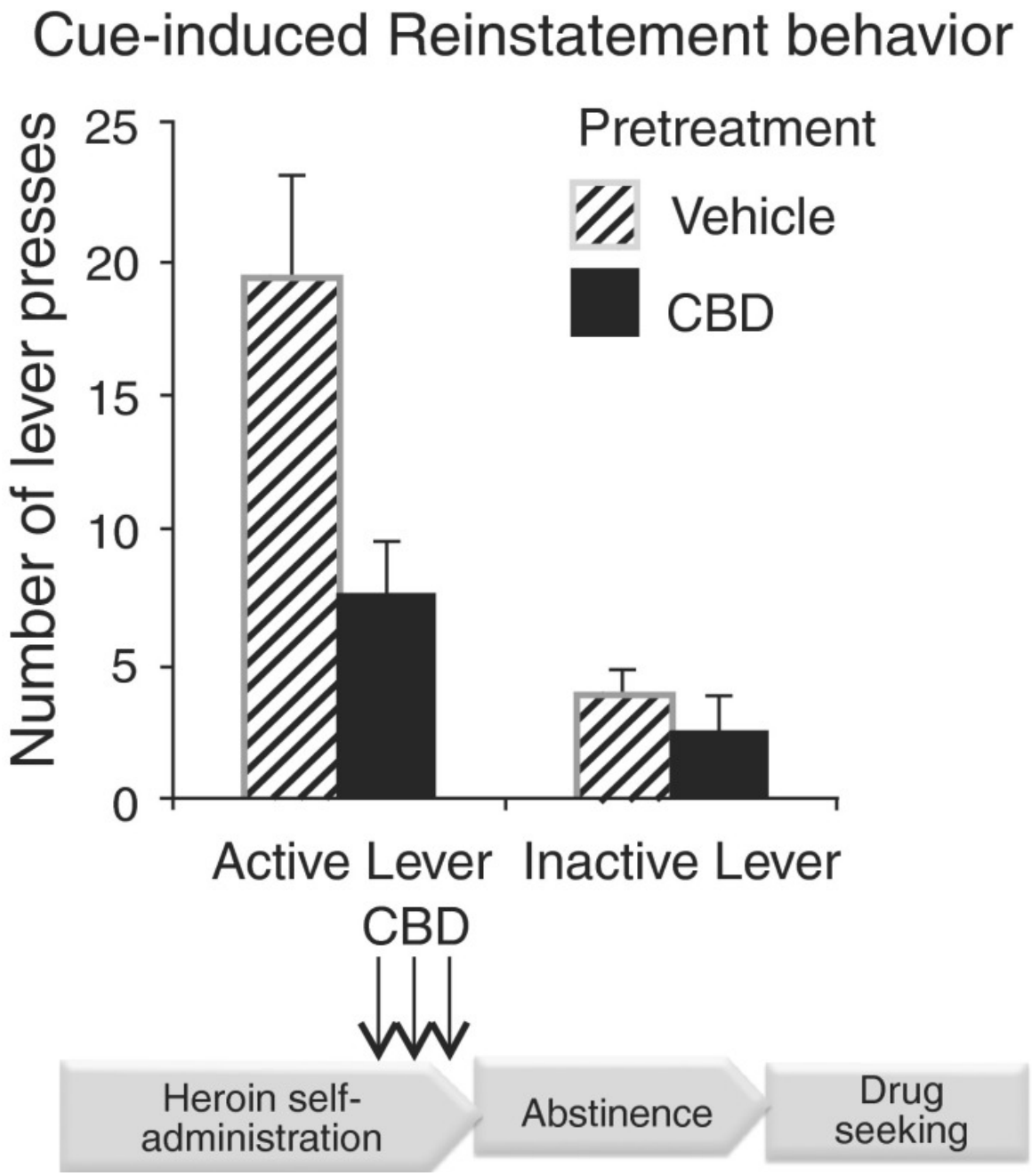
Hurd YL[1], Yoon M[2], Manini AF[3], Hernandez S[3], Olmedo R[3], Ostman M[4], Jutras-Aswad D[5].

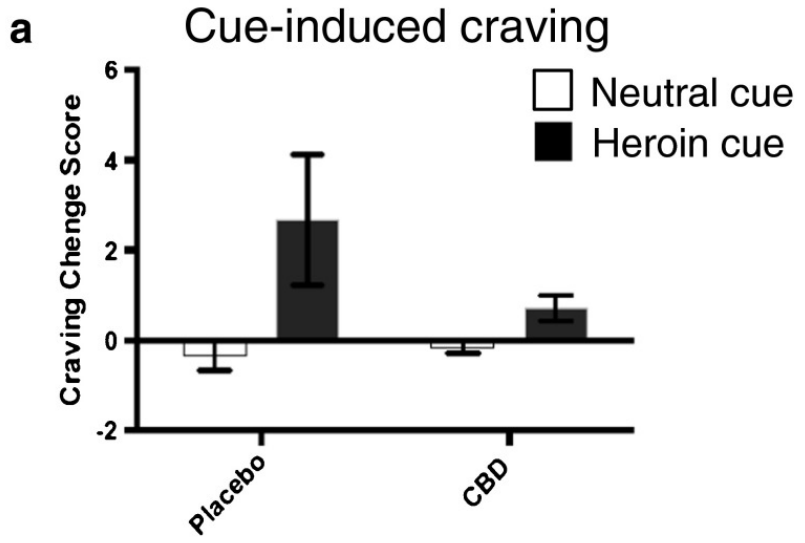
Abstract

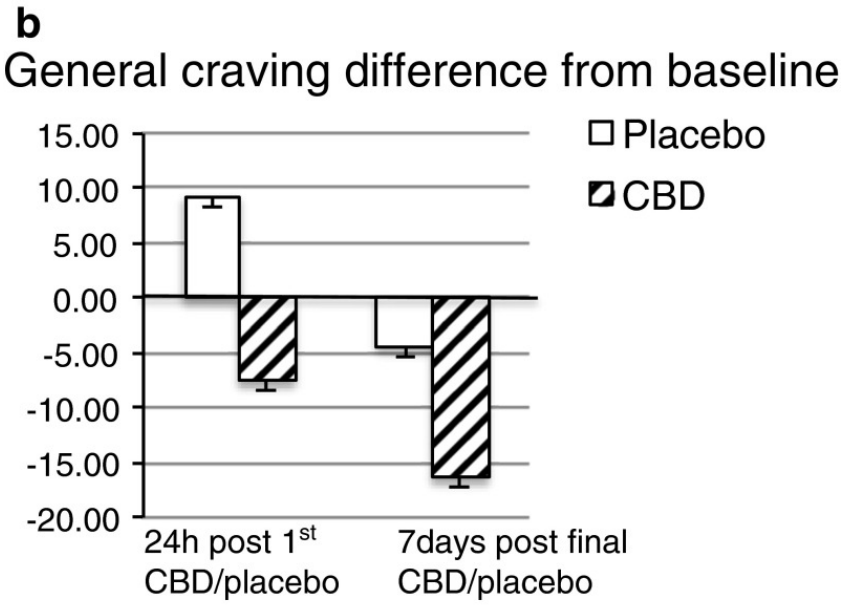
Multiple cannabinoids derived from the marijuana plant have potential therapeutic benefits but most have not been well investigated, despite the widespread legalization of medical marijuana in the USA and other countries. Therapeutic indications will depend on determinations as to which of the multiple cannabinoids, and other biologically active chemicals that are present in the marijuana plant, can be developed to treat specific symptoms and/or diseases. Such insights are particularly critical for addiction disorders, where different phytocannabinoids appear to induce opposing actions that can confound the development of treatment interventions. Whereas Δ(9)-tetracannabinol has been well documented to be rewarding and to enhance sensitivity to other drugs, cannabidiol (CBD), in contrast, appears to have low reinforcing properties with limited abuse potential and to inhibit drug-seeking behavior. Other considerations such as CBD's anxiolytic properties and minimal adverse side effects also support its potential viability as a treatment option for a variety of symptoms associated with drug addiction. However, significant research is still needed as CBD investigations published to date primarily relate to its effects on opioid drugs, and CBD's efficacy at different phases of the abuse cycle for different classes of addictive substances remain largely understudied. Our paper provides an overview of preclinical animal and human clinical investigations, and presents preliminary clinical data that collectively sets a strong foundation in support of the further exploration of CBD as a therapeutic intervention against opioid relapse. As the legal landscape for medical marijuana unfolds, it is important to distinguish it from "medical CBD" and other specific cannabinoids, that can more appropriately be used to maximize the medicinal potential of the marijuana plant.

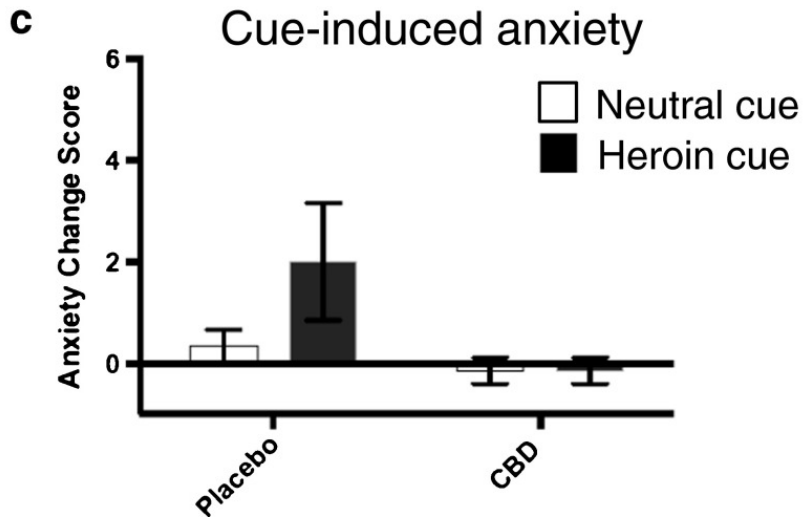
KEYWORDS:
Cannabis; Craving; Heroin; Human; Rat; THC
PMID: 26269227 PMCID: PMC4604178 DOI: 10.1007/s13311-015-0373-7
[Indexed for MEDLINE] Free PMC Article


OH
O
OH
OH
• Reward
• Drug seeking
• Anxiety (+/-)
• Sensitivity to other drugs of abuse
Δ-9-THC
• Reward
• Drug seeking
• Anxiety
• Sensitivity to other drugs of abuse
CBD


Cue-induced Reinstatement behavior
Number of lever presses
25
20
15
10
5
0
Pretreatment
Vehicle
CBD
Active Lever
Inactive Lever
CBD
Heroin self-administration
Abstinence
Drug seeking


a
Cue-induced craving
Craving Chenge Score
6
4
2
0
-2
Neutral cue
Heroin cue
Placebo
CBD


b
General craving difference from baseline
15.00
10.00
5.00
0.00
-5.00
-10.00
-15.00
-20.00
Placebo
CBD
24h post 1st CBD/placebo
7days post final CBD/placebo


c
Cue-induced anxiety
Anxiety Change Score
6
4
2
0
Neutral cue
Heroin cue
Placebo
CBD

CBD: addiction to substances AND behavior

Subst Abuse. 2015 May 21;9:33-8. doi: 10.4137/SART.S25081. eCollection 2015.

Cannabidiol as an Intervention for Addictive Behaviors: A Systematic Review of the Evidence.

Prud'homme M[1], Cata R[2], Jutras-Aswad D[1].

Author information

Abstract

Drug addiction is a chronically relapsing disorder characterized by the compulsive desire to use drugs and a loss of control over consumption. Cannabidiol (CBD), the second most abundant component of cannabis, is thought to modulate various neuronal circuits involved in drug addiction. The goal of this systematic review is to summarize the available preclinical and clinical data on the impact of CBD on addictive behaviors. MEDLINE and PubMed were searched for English and French language articles published before 2015. In all, 14 studies were found, 9 of which were conducted on animals and the remaining 5 on humans. A limited number of preclinical studies suggest that CBD may have therapeutic properties on opioid, cocaine, and psychostimulant addiction, and some preliminary data suggest that it may be beneficial in cannabis and tobacco addiction in humans. Further studies are clearly necessary to fully evaluate the potential of CBD as an intervention for addictive disorders.

KEYWORDS:
addictive behaviors; cannabidiol; drug addiction; review; treatment
PMID:
26056464
PMCID:
PMC4444130
DOI:
10.4137/SART.S25081
Free PMC Article

CBD: a motivator!

Annu Rev Neurosci. 2016 Jul 8;39:1-17. doi: 10.1146/annurev-neuro-070815-014038. Epub 2016 Feb 24.

Beyond the CB1 Receptor: Is Cannabidiol the Answer for Disorders of Motivation?

Zlebnik NE[1], Cheer JF[1,2].

Author information

Abstract

The Cannabis sativa plant has been used to treat various physiological and psychiatric conditions for millennia. Current research is focused on isolating potentially therapeutic chemical constituents from the plant for use in the treatment of many central nervous system disorders. Of particular interest is the primary nonpsychoactive constituent cannabidiol (CBD). Unlike Δ(9)-tetrahydrocannabinol (THC), CBD does not act through the cannabinoid type 1 (CB1) receptor but has many other receptor targets that may play a role in psychiatric disorders. Here we review preclinical and clinical data outlining the therapeutic efficacy of CBD for the treatment of motivational disorders such as drug addiction, anxiety, and depression. Across studies, findings suggest promising treatment effects and potentially overlapping mechanisms of action for CBD in these disorders and indicate the need for further systematic investigation of the viability of CBD as a psychiatric pharmacotherapy.

KEYWORDS:
THC; addiction; anxiety; cannabidiol; depression; reward; Δ9-tetrahydrocannabinol
PMID:
27023732
PMCID:
PMC5818147
DOI:
10.1146/annurev-neuro-070815-014038
[Indexed for MEDLINE]
Free PMC Article

CBD: sleep depravation, amphetamine relapse

Prog Neuropsychopharmacol Biol Psychiatry. 2018 Mar 2;82:307-313. doi: 10.1016/j.pnpbp.2017.08.022. Epub 2017 Sep 1.

Cannabidiol inhibits priming-induced reinstatement of methamphetamine in REM sleep deprived rats.

Karimi-Haghighi S[1], Haghparast A[2].

Abstract

Methamphetamine (METH) is a widely abused and a severely addictive psychostimulant. Relapse is the main cause of concern when treating addiction. It could manifest after a long period of abstinence. Previous studies showed that there is a strong connection between sleep impairment and relapse. Also, it has been reported that cannabidiol might be a potential treatment for drug craving and relapse. In this study, we used conditioned place preference (CPP) to investigate whether Cannabidiol (CBD), a phytocannabinoid, can prevent METH-induced reinstatement in Rapid Eye Movement Sleep Deprived (RSD) rats. In order to induce CPP, the animals were given METH (1mg/kg; sc) for five days. The effective priming dose of METH (0.5mg/kg, sc) reinstated the extinguished METH-induced CPP. In order to investigate the effect of RSD on METH-induced reinstatement, we used the inverted flowerpot technique to deprive the rats of REM sleep. We found that 24h-RSD could facilitate priming-induced reinstatement of METH. In addition to this, the ICV administration of CBD 10μg/5μl could suppress the METH-induced reinstatement even in RSD rats. In conclusion, the administration of CBD 10μg/5μl effectively prevents METH-induced CPP, even in a condition of stress. CBD can be considered an agent that reduces the risk of the relapse; however, this requires more investigation.

KEYWORDS:
Cannabidiol; Methamphetamine; REM sleep deprivation; Rat; Reinstatement; Reward
PMID:
28870635
DOI:
10.1016/j.pnpbp.2017.08.022

CBD: reduces tobacco use

Addict Behav. 2013 Sep;38(9):2433-6. doi: 10.1016/j.addbeh.2013.03.011. Epub 2013 Apr 1.

Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings.

Morgan CJ[1], Das RK, Joye A, Curran HV, Kamboj SK.

Abstract

The role of the endocannabinoid system in nicotine addiction is being increasingly acknowledged. We conducted a pilot, randomised double blind placebo controlled study set out to assess the impact of the ad-hoc use of cannabidiol (CBD) in smokers who wished to stop smoking. 24 smokers were randomised to receive an inhaler of CBD (n=12) or placebo (n=12) for one week, they were instructed to use the inhaler when they felt the urge to smoke. Over the treatment week, placebo treated smokers showed no differences in number of cigarettes smoked. In contrast, those treated with CBD significantly reduced the number of cigarettes smoked by ~40% during treatment. Results also indicated some maintenance of this effect at follow-up. These preliminary data, combined with the strong preclinical rationale for use of this compound, suggest CBD to be a potential treatment for nicotine addiction that warrants further exploration.

PMID:
23685330
DOI:
10.1016/j.addbeh.2013.03.011

CBD: amphetamine relapse

J Psychopharmacol. 2018 Dec;32(12):1369-1378. doi: 10.1177/0269881118799954. Epub 2018 Sep 27.

Cannabidiol treatment reduces the motivation to self-administer methamphetamine and methamphetamine-primed relapse in rats.

Hay GL[1], Baracz SJ[1,2], Everett NA[1], Roberts J[1], Costa PA[1], Arnold JC[3,4], McGregor IS[2,4], Cornish JL[1].

Abstract

BACKGROUND:: Methamphetamine is an addictive stimulant that can cause many adverse physical, psychological and psychosocial effects. Preliminary evidence shows cannabidiol, a non-intoxicating constituent of the cannabis plant, may have efficacy in treating opioid and nicotine dependence. However, no study has yet examined whether cannabidiol treatment might impact on methamphetamine addiction. **AIMS::** The current study investigated whether cannabidiol administration reduces the motivation to self-administer methamphetamine and relapse to methamphetamine-seeking behavior following abstinence. **METHODS::** Thirty-two male Sprague Dawley rats with implanted jugular vein catheters were initially trained to self-administer methamphetamine via lever press during two-hour sessions on a fixed ratio 1 schedule of reinforcement. Rats in experiment 1 (n=16) then advanced to a progressive ratio reinforcement schedule to examine the effects of cannabidiol (0, 20, 40, and 80 mg/kg intraperitoneal) on motivation to self-administer methamphetamine. Rats in experiment 2 (n=16) were tested for cannabidiol effects on methamphetamine-primed reinstatement following extinction. **RESULTS::** Cannabidiol (80 mg/kg, but not 40 mg/kg, or 20 mg/kg) reduced the motivation to self-administer methamphetamine and attenuated methamphetamine-primed relapse to methamphetamine-seeking behavior after extinction. **CONCLUSION::** This is the first demonstration that cannabidiol can reduce the motivation to seek and consume methamphetamine, and suggests that cannabidiol might be worth trialing as a novel pharmacotherapy for methamphetamine dependence.

KEYWORDS: Addiction; cannabidiol; methamphetamine; relapse; self-administration
PMID: 30260267 DOI: 10.1177/0269881118799954

CBD: antidote to THC

Front Psychiatry. 2013 Oct 16;4:130. doi: 10.3389/fpsyt.2013.00130.

Does Cannabidiol Protect Against Adverse Psychological Effects of THC?

Niesink RJ[1], van Laar MW.

Abstract

The recreational use of cannabis can have persistent adverse effects on mental health. Delta-9-tetrahydrocannabinol (THC) is the main psychoactive constituent of cannabis, and most, if not all, of the effects associated with the use of cannabis are caused by THC. Recent studies have suggested a possible protective effect of another cannabinoid, cannabidiol (CBD). A literature search was performed in the bibliographic databases PubMed, PsycINFO, and Web of Science using the keyword "cannabidiol." After removing duplicate entries, 1295 unique titles remained. Based on the titles and abstracts, an initial selection was made. The reference lists of the publications identified in this manner were examined for additional references. Cannabis is not a safe drug. Depending on how often someone uses, the age of onset, the potency of the cannabis that is used and someone's individual sensitivity, the recreational use of cannabis may cause permanent psychological disorders. Most recreational users will never be faced with such persistent mental illness, but in some individuals cannabis use leads to undesirable effects: cognitive impairment, anxiety, paranoia, and increased risks of developing chronic psychosis or drug addiction. Studies examining the protective effects of CBD have shown that CBD can counteract the negative effects of THC. However, the question remains of how the laboratory results translate to the types of cannabis that are encountered by real-world recreational users.

KEYWORDS:
anxiety; cannabidiol; cannabis; cognition; drug dependence; psychosis; tetrahydrocannabinol
PMID:
24137134
PMCID:
PMC3797438
DOI:
10.3389/fpsyt.2013.00130
Free PMC Article

CBD: Alcohol

Alcohol Clin Exp Res. 2019 Jan 30. doi: 10.1111/acer.13964. [Epub ahead of print]

Cannabidiol as a novel candidate alcohol use disorder pharmacotherapy: a systematic review.

Turna J[1,2], Syan SK[2,3,4], Frey BN[4,5], Rush B[6], Costello J[6], Weiss M[7], MacKillop J[1,2,3,4,6].

Abstract

There is substantial interest in the therapeutic potential of cannabidiol (CBD), a non-psychoactive cannabinoid found in plants of the genus Cannabis. The goal of the current systematic review was to characterize the existing literature on this topic and to evaluate the credibility of CBD as a candidate pharmacotherapy for alcohol use disorder (AUD). Using a comprehensive search strategy, 303 unique potential articles were identified and 12 ultimately met criteria for inclusion (8 using rodent models, 3 using healthy adult volunteers, and 1 using cell culture). In both rodent and cell culture models, CBD was found to exert a neuroprotective effect against adverse alcohol consequences on the hippocampus. In rodent models, CBD was found to attenuate alcohol-induced hepatotoxicity, specifically, alcohol-induced steatosis. Finally, findings from preclinical rodent models also indicate that CBD attenuates cue-elicited and stress-elicited alcohol-seeking, alcohol self-administration, withdrawal-induced convulsions, and impulsive discounting of delayed rewards. In human studies, CBD was well tolerated and did not interact with the subjective effects of alcohol. Collectively, given its favorable effects on alcohol-related harms and addiction phenotypes in preclinical models, CBD appears to have promise as a candidate AUD pharmacotherapy. This is further bolstered by the absence of abuse liability and its general tolerability. A clear limitation to the literature is the paucity of human investigations. Human preclinical and clinical studies are needed to determine whether these positive effects in model systems substantively translate into clinically-relevant outcomes. This article is protected by copyright. All rights reserved.

KEYWORDS: CBD ; alcohol; alcohol use disorder; cannabidiol; pharmacotherapy
PMID: 30698831 DOI: 10.1111/acer.13964

CBD: balances against THC

Neuropsychopharmacology. 2010 Aug;35(9):1879-85. doi: 10.1038/npp.2010.58. Epub 2010 Apr 28.

Cannabidiol attenuates the appetitive effects of Delta 9-tetrahydrocannabinol in humans smoking their chosen cannabis.

Morgan CJ[1], Freeman TP, Schafer GL, Curran HV.

Abstract

Worldwide cannabis dependence is increasing, as is the concentration of Delta(9)-tetrahydrocannabinol (THC) in street cannabis. At the same time, the concentration of the second most abundant cannabinoid in street cannabis, cannabidiol (CBD), is decreasing. These two cannabinoids have opposing effects both pharmacologically and behaviorally when administered in the laboratory. No research has yet examined how the ratio of these constituents impacts on the appetitive/reinforcing effects of cannabis in humans. A total of 94 cannabis users were tested 7 days apart, once while non-intoxicated and once while acutely under the influence of their own chosen smoked cannabis on dependence-related measures. Using an unprecedented methodology, a sample of cannabis (as well as saliva) was collected from each user and analyzed for levels of cannabinoids. On the basis of CBD : THC ratios in the cannabis, individuals from the top and bottom tertiles were directly compared on indices of the reinforcing effects of drugs, explicit liking, and implicit attentional bias to drug stimuli. When intoxicated, smokers of high CBD : THC strains showed reduced attentional bias to drug and food stimuli compared with smokers of low CBD : THC. Those smoking higher CBD : THC strains also showed lower self-rated liking of cannabis stimuli on both test days. Our findings suggest that CBD has potential as a treatment for cannabis dependence. The acute modulation of the incentive salience of drug cues by CBD may possibly generalize to a treatment for other addictive disorders.

PMID: 20428110 PMCID: PMC2906701 DOI: 10.1038/npp.2010.58
[Indexed for MEDLINE]
Free PMC Article

CBD: tobacco

Addiction. 2018 May 1. doi: 10.1111/add.14243. [Epub ahead of print]

Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal.

Hindocha C[1], Freeman TP[1,2], Grabski M[1,3], Stroud JB[1], Crudgington H[1], Davies AC[1], Das RK[1], Lawn W[1], Morgan CJA[1,4], Curran HV[1].

Abstract

BACKGROUND AND AIMS: Cannabidiol (CBD), a non-intoxicating cannabinoid found in cannabis, may be a promising novel smoking cessation treatment due to its anxiolytic properties, minimal side effects and research showing that it may modify drug cue salience. We used an experimental medicine approach with dependent cigarette smokers to investigate if (1) overnight nicotine abstinence, compared with satiety, will produce greater attentional bias (AB), higher pleasantness ratings of cigarette-related stimuli and increased craving and withdrawal; and (2) CBD in comparison to placebo, would attenuate AB, pleasantness of cigarette-related stimuli, craving and withdrawal and not produce any side effects. **DESIGN:** Randomized, double-blind cross-over study with a fixed satiated session followed by two overnight abstinent sessions. **SETTING:** UK laboratory. **PARTICIPANTS:** Thirty non-treatment-seeking, dependent cigarette smokers recruited from the community. **INTERVENTION AND COMPARATOR:** 800 mg oral CBD, or matched placebo (PBO) in a counterbalanced order MEASUREMENTS: AB to pictorial tobacco cues was recorded using a visual probe task and an explicit rating task. Withdrawal, craving, side effects, heart rate and blood pressure were assessed repeatedly. **FINDINGS:** When participants received PBO, tobacco abstinence increased AB (P = 0.001, d = 0.789) compared with satiety. However, CBD reversed this effect, such that automatic AB was directed away from cigarette cues (P = 0.007, d = 0.704) and no longer differed from satiety (P = 0.82). Compared with PBO, CBD also reduced explicit pleasantness of cigarette images (P = 0.011; d = 0.514). Craving (Bayes factor = 7.08) and withdrawal (Bayes factor = 6.95) were unaffected by CBD, but greater in abstinence compared with satiety. Systolic blood pressure decreased under CBD during abstinence. **CONCLUSIONS:** A single 800-mg oral dose of cannabidiol reduced the salience and pleasantness of cigarette cues, compared with placebo, after overnight cigarette abstinence in dependent smokers. Cannabidiol did not influence tobacco craving or withdrawal or any subjectively rated side effects.

KEYWORDS:
Abstinence; attentional bias; cannabidiol; cigarette dependence; craving; withdrawal
PMID:

29714034
PMCID:
PMC6099309
DOI:
10.1111/add.14243
Free PMC Article

CBD: cocaine addiction

Neuropharmacology. 2018 Dec;143:163-175. doi: 10.1016/j.neuropharm.2018.09.043. Epub 2018 Sep 28.

Repeated Cannabidiol treatment reduces cocaine intake and modulates neural proliferation and CB1R expression in the mouse hippocampus.

Luján MÁ[1], Castro-Zavala A[1], Alegre-Zurano L[1], Valverde O[2].

Abstract

Cannabinoid derivatives have shown promising results for treating neuropsychiatric disorders, including drug addiction. Recent studies on the therapeutic effects of Cannabidiol (CBD) on drug abuse showed mixed results, especially with psychostimulant substances such as cocaine. To determine whether CBD can attenuate cocaine reinforcement, we assessed behavioural responses induced by cocaine in mice, using the behavioural sensitization, conditioned place preference and intravenous self-administration paradigms. We show that repeated CBD treatment produces anxiolytic effects in the elevated plus maze test, increases the discrimination index of the novel object recognition task and attenuates cocaine-induced conditioned place preference but does not affect behavioural sensitization. CBD reduced cocaine voluntary consumption and progressive ratio breaking point in the self-administration paradigm, but not drug-induced reinstatement. In parallel, CBD increased expression of type 1 cannabinoid receptor, MAPK-CREB phosphorylation, BDNF expression, and neural cell proliferation in the hippocampus, and reduced the GluA1/2 AMPA subunit receptor ratio in the striatum. In summary, we show that CBD can modulate some behavioural and molecular manifestations of cocaine reinforcement. Moreover, our findings show that CBD has pro-neurogenic effects also in cocaine consuming animals. Overall, this novel evidence provides new perspectives to use CBD as a therapeutic tool.

KEYWORDS:
Addiction; Cannabidiol; Cocaine; Neurogenesis; Self-administration

CBD: prevents relapse

Neuropsychopharmacology. 2018 Sep;43(10):2036-2045. doi: 10.1038/s41386-018-0050-8. Epub 2018 Mar 22.

Unique treatment potential of cannabidiol for the prevention of relapse to drug use: preclinical proof of principle.

Gonzalez-Cuevas G[1,2], Martin-Fardon R[1], Kerr TM[1], Stouffer DG[1], Parsons LH[1], Hammell DC[3], Banks SL[4], Stinchcomb AL[3], Weiss F[5].

Abstract

Cannabidiol (CBD), the major non-psychoactive constituent of Cannabis sativa, has received attention for therapeutic potential in treating neurologic and psychiatric disorders. Recently, CBD has also been explored for potential in treating drug addiction. Substance use disorders are chronically relapsing conditions and relapse risk persists for multiple reasons including craving induced by drug contexts, susceptibility to stress, elevated anxiety, and impaired impulse control. Here, we evaluated the "anti-relapse" potential of a transdermal CBD preparation in animal models of drug seeking, anxiety and impulsivity. Rats with alcohol or cocaine self-administration histories received transdermal CBD at 24 h intervals for 7 days and were tested for context and stress-induced reinstatement, as well as experimental anxiety on the elevated plus maze. Effects on impulsive behavior were established using a delay-discounting task following recovery from a 7-day dependence-inducing alcohol intoxication regimen. CBD attenuated context-induced and stress-induced drug seeking without tolerance, sedative effects, or interference with normal motivated behavior. Following treatment termination, reinstatement remained attenuated up to ≈5 months although plasma and brain CBD levels remained detectable only for 3 days. CBD also reduced experimental anxiety and prevented the development of high impulsivity in rats with an alcohol dependence history. The results provide proof of principle supporting potential of CBD in relapse prevention along two dimensions: beneficial actions across several vulnerability states and long-lasting effects with only brief treatment. The findings also inform the ongoing medical marijuana debate concerning medical benefits of non-psychoactive cannabinoids and their promise for development and use as therapeutics.

PMID: 29686308 PMCID: PMC6098033 DOI: 10.1038/s41386-018-0050-8
Free PMC Article

CBD: Panic-olytic

Psychopharmacology (Berl). 2013 Mar;226(1):13-24. doi: 10.1007/s00213-012-2878-7. Epub 2012 Sep 25.

Involvement of serotonin-mediated neurotransmission in the dorsal periaqueductal gray matter on cannabidiol chronic effects in panic-like responses in rats.

Campos AC[1], de Paula Soares V, Carvalho MC, Ferreira FR, Vicente MA, Brandão ML, Zuardi AW, Zangrossi H Jr, Guimarães FS.

Abstract

RATIONALE: Cannabidiol (CBD) is a non-psychotomimetic constituent of Cannabis sativa plant that promotes antianxiety and anti-panic effects in animal models after acute systemic or intra-dorsal periaqueductal gray (DPAG) administration. However, the effects of CBD repeated administration, and the possible mechanisms involved, in animal models of anxiety- and panic-related responses remain poorly understood. **OBJECTIVE:** The present study evaluates the role of the serotonergic neurotransmission within the DPAG in the modulation of escape responses of rats chronically treated with CBD. **METHODS:** Male Wistar rats received acute or repeated (5 mg/Kg/daily/21 days) administration of CBD and were submitted to the elevated T-maze (ETM). We also investigated if CBD effects on the ETM depend on facilitation of 5-HT1A-mediated neurotransmission in the DPAG. To this latter aim, we verified if these effects would be prevented by intra-DPAG injection of the 5-HT1A receptor antagonist WAY100635 (0.37 nmol/0.2 μL). Also, we verified, by in vivo microdialysis, if CBD chronic treatment increases serotonin (5-HT) release and, by quantitative polymerase chain reaction, if there are changes in 5HT-1A or 5HT-2C mRNA expression in DPAG. **RESULTS:** The results showed that repeated but not acute peripheral administration of CBD decreases escape responses in the ETM, suggesting a panicolytic effect. This treatment did not change 5HT-1A or 5-HT-2C receptor mRNA expression nor modify serotonin extracellular concentrations in the DPAG. CBD effects were prevented by DPAG injection of the 5-HT1A receptor antagonist. **CONCLUSIONS:**Together, these findings suggest that repeated treatment with CBD induces anti-panic effects by acting on 5-HT1A receptors in DPAG.

PMID: 23007604 DOI: 10.1007/s00213-012-2878-7 [Indexed for MEDLINE]

CBD: Counteracts morphine

Addict Biol. 2013 Mar;18(2):286-96. doi: 10.1111/j.1369-1600.2012.00483.x. Epub 2012 Aug 2.

Cannabidiol inhibits the reward-facilitating effect of morphine: involvement of 5-HT1A receptors in the dorsal raphe nucleus.

Katsidoni V[1], Anagnostou I, Panagis G.

Author information

Abstract

Cannabidiol is a non-psychotomimetic constituent of Cannabis sativa, which induces central effects in rodents. It has been shown that cannabidiol attenuates cue-induced reinstatement of heroin seeking. However, to the best of our knowledge, its effects on brain stimulation reward and the reward-facilitating effects of drugs of abuse have not yet been examined. Therefore, we investigated the effects of cannabidiol on brain reward function and on the reward-facilitating effect of morphine and cocaine using the intracranial self-stimulation (ICSS) paradigm. Rats were prepared with a stimulating electrode into the medial forebrain bundle (MFB), and a guide cannula into the dorsal raphe (microinjection experiments), and were trained to respond for electrical brain stimulation. A low dose of cannabidiol did not affect the reinforcing efficacy of brain stimulation, whereas higher doses significantly elevated the threshold frequency required for MFB ICSS. Both cocaine and morphine lowered ICSS thresholds. Cannabidiol inhibited the reward-facilitating effect of morphine, but not cocaine. This effect was reversed by pre-treatment with an intra-dorsal raphe injection of the selective 5-HT1A receptor antagonist WAY-100635. The present findings indicate that cannabidiol does not exhibit reinforcing properties in the ICSS paradigm at any of the doses tested, while it decreases the reward-facilitating effects of morphine. These effects were mediated by activation of 5-HT1A receptors in the dorsal raphe. Our results suggest that cannabidiol interferes with brain reward mechanisms responsible for the expression of the acute reinforcing properties of opioids, thus indicating that cannabidiol may be clinically useful in attenuating the rewarding effects of opioids.

PMID:
22862835
DOI:
10.1111/j.1369-1600.2012.00483.x
[Indexed for MEDLINE]

CBD: non-addictive

Drug Alcohol Depend. 2017 Mar 1;172:9-13. doi: 10.1016/j.drugalcdep.2016.11.030. Epub 2016 Dec 14.

Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers.

Babalonis S[1], Haney M[2], Malcolm RJ[3], Lofwall MR[4], Votaw VR[5], Sparenborg S[6], Walsh SL[4].

Abstract

BACKGROUND:
Cannabidiol (CBD) is a naturally occurring constituent of the marijuana plant. In the past few years, there has been great interest in the therapeutic effects of isolated CBD and it is currently being explored for numerous disease conditions (e.g., pain, epilepsy, cancer, various drug dependencies). However, CBD remains a Schedule I drug on the U.S. Controlled Substances Act (CSA). Despite its status, there are no well-controlled data available regarding its abuse liability. **METHODS:** Healthy, frequent marijuana users (n=31) were enrolled in this within subject, randomized, placebo-controlled, double-blind, multisite study that administered oral cannabidiol (0, 200, 400, 800mg) alone and in combination with smoked marijuana (0.01%, 5.3-5.8% THC). Participants received one dose combination across 8 once-weekly outpatient sessions (7.5h). The primary findings on the drug interaction effects were previously reported (Haney et al., 2016). The present study is a secondary analysis of the data to examine the abuse liability profile of oral cannabidiol (200, 400, 800mg) in comparison to oral placebo and active smoked marijuana (5.3-5.8% THC). **RESULTS:** Active marijuana reliably produced abuse-related subjective effects (e.g., high) ($p<0.05$). However, CBD was placebo-like on all measures collected ($p>0.05$). **CONCLUSIONS:** Overall, CBD did not display any signals of abuse liability at the doses tested and these data may help inform U.S. regulatory decisions regarding CBD schedule on the CSA.

KEYWORDS: Abuse liability; CBD; Cannabidiol; Human; Smoked marijuana
PMID: 28088032 PMCID: PMC5361620 DOI: 10.1016/j.drugalcdep.2016.11.030
[Indexed for MEDLINE] Free PMC Article