CBD: antiinflammatory, repair from injury

Naunyn Schmiedebergs Arch Pharmacol. 2004 Mar;369(3):294-9. Epub 2004 Feb 12.

Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw.

Costa B[1], Colleoni M, Conti S, Parolaro D, Franke C, Trovato AE, Giagnoni G.

Abstract

Cannabidiol, the major non-psychoactive component of marijuana, has various pharmacological actions of clinical interest. It is reportedly effective as an anti-inflammatory and anti-arthritic in murine collagen-induced arthritis. The present study examined the anti-inflammatory and anti-hyperalgesic effects of cannabidiol, administered orally (5-40 mg/kg) once a day for 3 days after the onset of acute inflammation induced by intraplantar injection of 0.1 ml carrageenan (1% w/v in saline) in the rat. At the end of the treatment prostaglandin E2 (PGE2) was assayed in the plasma, and cyclooxygenase (COX) activity, production of nitric oxide (NO; nitrite/nitrate content), and of other oxygen-derived free radicals (malondialdehyde) in inflamed paw tissues. All these markers were significantly increased following carrageenan. Thermal hyperalgesia, induced by carrageenan and assessed by the plantar test, lasted 7 h. Cannabidiol had a time- and dose-dependent anti-hyperalgesic effect after a single injection. Edema following carrageenan peaked at 3 h and lasted 72 h; a single dose of cannabidiol reduced edema in a dose-dependent fashion and subsequent daily doses caused further time- and dose-related reductions. There were decreases in PGE2 plasma levels, tissue COX activity, production of oxygen-derived free radicals, and NO after three doses of cannabidiol. The effect on NO seemed to depend on a lower expression of the endothelial isoform of NO synthase. In conclusion, oral cannabidiol has a beneficial action on two symptoms of established inflammation: edema and hyperalgesia.

PMID:14963641 DOI: 10.1007/s00210-004-0871-3

CBD: osteoarthritis

Proc Natl Acad Sci U S A. 2000 Aug 15;97(17):9561-6.

The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis.

Malfait AM[1], Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldmann M.

Abstract

The therapeutic potential of cannabidiol (CBD), the major nonpsychoactive component of cannabis, was explored in murine collagen-induced arthritis (CIA). CIA was elicited by immunizing DBA/1 mice with type II collagen (CII) in complete Freund's adjuvant. The CII used was either bovine or murine, resulting in classical acute CIA or in chronic relapsing CIA, respectively. CBD was administered after onset of clinical symptoms, and in both models of arthritis the treatment effectively blocked progression of arthritis. CBD was equally effective when administered i.p. or orally. The dose dependency showed a bell-shaped curve, with an optimal effect at 5 mg/kg per day i.p. or 25 mg/kg per day orally. Clinical improvement was associated with protection of the joints against severe damage. Ex vivo, draining lymph node cells from CBD-treated mice showed a diminished CII-specific proliferation and IFN-gamma production, as well as a decreased release of tumor necrosis factor by knee synovial cells. In vitro effects of CBD included a dose-dependent suppression of lymphocyte proliferation, both mitogen-stimulated and antigen-specific, and the blockade of the Zymosan-triggered reactive oxygen burst by peritoneal granulocytes. It also was found that CBD administration was capable of blocking the lipopolysaccharide-induced rise in serum tumor necrosis factor in C57/BL mice. Taken together, these data show that CBD, through its combined immunosuppressive and anti-inflammatory actions, has a potent anti-arthritic effect in CIA.

PMCID: PMC16904 DOI: 10.1073/pnas.160105897

CBD: osteoarthritis

Pain. 2017 Dec;158(12):2442-2451. doi: 10.1097/j.pain.0000000000001052.

Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis.

Philpott HT[1], O'Brien M, McDougall JJ.

Abstract

Osteoarthritis (OA) is a multifactorial joint disease, which includes joint degeneration, intermittent inflammation, and peripheral neuropathy. Cannabidiol (CBD) is a noneuphoria producing constituent of cannabis that has the potential to relieve pain. The aim of this study was to determine whether CBD is anti-nociceptive in OA, and whether inhibition of inflammation by CBD could prevent the development of OA pain and joint neuropathy. Osteoarthritis was induced in male Wistar rats (150-175 g) by intra-articular injection of sodium monoiodoacetate (MIA; 3 mg). On day 14 (end-stage OA), joint afferent mechanosensitivity was assessed using in vivo electrophysiology, whereas pain behaviour was measured by von Frey hair algesiometry and dynamic incapacitance. To investigate acute joint inflammation, blood flow and leukocyte trafficking were measured on day 1 after MIA. Joint nerve myelination was calculated by G-ratio analysis. The therapeutic and prophylactic effects of peripheral CBD (100-300 μg) were assessed. In end-stage OA, CBD dose-dependently decreased joint afferent firing rate, and increased withdrawal threshold and weight bearing ($P < 0.0001$; $n = 8$). Acute, transient joint inflammation was reduced by local CBD treatment ($P < 0.0001$; $n = 6$). Prophylactic administration of CBD prevented the development of MIA-induced joint pain at later time points ($P < 0.0001$; $n = 8$), and was also found to be neuroprotective ($P < 0.05$; $n = 6$-8). The data presented here indicate that local administration of CBD blocked OA pain. Prophylactic CBD treatment prevented the later development of pain and nerve damage in these OA joints. These findings suggest that CBD may be a safe, useful therapeutic for treating OA joint neuropathic pain.

PMID: 28885454 PMCID: PMC5690292 DOI: 10.1097/j.pain.0000000000001052
[Indexed for MEDLINE] Free PMC Article

CBD: injury recovery, collagen crosslinking, fracture healing

J Bone Miner Res. 2015 Oct;30(10):1905-13. doi: 10.1002/jbmr.2513. Epub 2015 May 10.

Cannabidiol, a Major Non-Psychotropic Cannabis Constituent Enhances Fracture Healing and Stimulates Lysyl Hydroxylase Activity in Osteoblasts.

Kogan NM[1], Melamed E[1], Wasserman E[1], Raphael B[1,2], Breuer A[3], Stok KS[4], Sondergaard R[4], Escudero AV[4], Baraghithy S[1], Attar-Namdar M[1], Friedlander-Barenboim S[5], Mathavan N[6,7], Isaksson H[6,7], Mechoulam R[3], Müller R[4], Bajayo A[1], Gabet Y[2], Bab I[1].

Abstract

Cannabinoid ligands regulate bone mass, but skeletal effects of cannabis (marijuana and hashish) have not been reported. Bone fractures are highly prevalent, involving prolonged immobilization and discomfort. Here we report that the major non-psychoactive cannabis constituent, cannabidiol (CBD), enhances the biomechanical properties of healing rat mid-femoral fractures. The maximal load and work-to-failure, but not the stiffness, of femurs from rats given a mixture of CBD and Δ(9) -tetrahydrocannabinol (THC) for 8 weeks were markedly increased by CBD. This effect is not shared by THC (the psychoactive component of cannabis), but THC potentiates the CBD stimulated work-to-failure at 6 weeks postfracture followed by attenuation of the CBD effect at 8 weeks. Using micro-computed tomography (μCT), the fracture callus size was transiently reduced by either CBD or THC 4 weeks after fracture but reached control level after 6 and 8 weeks. The callus material density was unaffected by CBD and/or THC. By contrast, CBD stimulated mRNA expression of Plod1 in primary osteoblast cultures, encoding an enzyme that catalyzes lysine hydroxylation, which is in turn involved in collagen crosslinking and stabilization. Using Fourier transform infrared (FTIR) spectroscopy we confirmed the increase in collagen crosslink ratio by CBD, which is likely to contribute to the improved biomechanical properties of the fracture callus. Taken together, these data show that CBD leads to improvement in fracture healing and demonstrate the critical mechanical role of collagen crosslinking enzymes.
KEYWORDS:CANNABIDIOL; COLLAGEN CROSSLINKING; FRACTURE HEALING; FTIR; LYSYL HYDROXYLASE; μCT
PMID:25801536DOI:10.1002/jbmr.2513[Indexed for MEDLINE]Free full text

CBD: bone loss

Eur J Pharmacol. 2017 Aug 15;809:13-19. doi: 10.1016/j.ejphar.2017.05.011. Epub 2017 May 4.

Cannabidiol administration reduces sublesional cancellous bone loss in rats with severe spinal cord injury.

Li D[1], Lin Z[1], Meng Q[2], Wang K[1], Wu J[1], Yan H[3].

Abstract

Patients with spinal cord injury (SCI) undergo severe loss of bone mineral below the level of lesion, and data on available treatment options after SCI is scarce. The aim of this work was to investigate the therapeutic effect of cannabidiol (CBD), a non-psychoactive cannabis, on sublesional bone loss in a rat model of SCI. The adult male rats were exposed to surgical transection of the cord and treated with CBD for consecutive 14 days. It was found that CBD treatment elevated the serum levels of osteocalcin, reduced the serum levels of collagen type I cross-linked C-telopeptide, and enhanced bone mineral density of tibiae and femurs. Treatment of SCI rats with CBD enhanced bone volume, trabecular thickness, and trabecular number, and reduced trabecular separation in proximal tibiae, and increased ultimate compressive load, stiffness, and energy to max force of femoral diaphysis. Treatment of SCI rats with CBD upregulated mRNA expression of alkaline phosphatase and osteoprotegerin and downregulated mRNA expression of receptor activator of NF-κB ligand and tartrate-resistant acid phosphatase in femurs. Furthermore, treatment of SCI rats with CBD enhanced mRNA expression of wnt3a, Lrp5 and ctnnb1 in femurs. In conclusion, CBD administration attenuated SCI-induced sublesional cancellous bone loss.

KEYWORDS:
Bone loss; Cannabidiol; Spinal cord injury; Wnt/β-catenin
PMID:
28479140
DOI:
10.1016/j.ejphar.2017.05.011

CBD: Injury wound healing

Eur J Pharmacol. 2016 Sep 5;786:128-136. doi: 10.1016/j.ejphar.2016.06.006. Epub 2016 Jun 3.

Pharmacological activation of cannabinoid 2 receptor attenuates inflammation, fibrogenesis, and promotes re-epithelialization during skin wound healing.

Wang LL1, Zhao R1, Li JY1, Li SS1, Liu M1, Wang M1, Zhang MZ1, Dong WW1, Jiang SK1, Zhang M1, Tian ZL1, Liu CS2, Guan DW3.
Author information

Abstract
Previous studies showed that cannabinoid 2 (CB2) receptor is expressed in multiple effector cells during skin wound healing. Meanwhile, its functional involvement in inflammation, fibrosis, and cell proliferation in other organs and skin diseases implied CB2 receptor might also regulate skin wound healing. To verify this hypothesis, mice excisional wounds were created and treated with highly selective CB2 receptor agonist GP1a (1-(2,4-dichlorophenyl)-6-methyl- N-piperidin-1-yl-4H-indeno[1,2-c]pyrazole-3-carboxamide) and antagonist AM630 ([6-iodo-2- methyl-1-(2-morpholin-4-ylethyl)indol-3-yl]-(4-methoxyphenyl)methanone) respectively. The inflammatory infiltration, cytokine expression, fibrogenesis, and wound re-epithelialization were analyzed. After CB2 receptor activation, neutrophil and macrophage infiltrations were reduced, and expressions of monocyte chemotactic protein (MCP)-1, stromal cell-derived factor (SDF)-1, Interleukin (IL)-6, IL-1β, tumor necrosis factor (TNF)-α, transforming growth factor (TGF)-β1 and vascular endothelial growth factor (VEGF)-A were decreased. Keratinocyte proliferation and migration were enhanced. Wound re-epithelialization was accelerated. Fibroblast accumulation and fibroblast-to-myofibroblast transformation were attenuated, and expression of pro-collagen I was decreased. Furthermore, HaCaT cells in vitro were treated with GP1a or AM630, which revealed that CB2 receptor activation promoted keratinocyte migration by inducing the epithelial to mesenchymal transition. These results, taken together, indicate that activating CB2 receptor could ameliorate wound healing by reducing inflammation, accelerating re-epithelialization, and attenuating scar formation. Thus, CB2 receptor agonist might be a novel perspective for skin wound therapy.

KEYWORDS: AM630 (PubChem CID: 4302963); Cannabinoid 2 receptor; Fibrogenesis; GP1a (PubChem CID: 10252734); Inflammation; Re-epithelialization; Skin wound healing
PMID: 27268717 DOI: 10.1016/j.ejphar.2016.06.006

CBD: disk degeneration

PLoS One. 2014 Dec 17;9(12):e113161. doi: 10.1371/journal.pone.0113161. eCollection 2014.

Protective effects of cannabidiol on lesion-induced intervertebral disc degeneration.

Silveira JW[1], Issy AC[1], Castania VA[1], Salmon CE[2], Nogueira-Barbosa MH[3], Guimarães FS[4], Defino HL[5], Del Bel E[1].

Author information

Abstract

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

PMID:
25517414
PMCID:
PMC4269422
DOI:
10.1371/journal.pone.0113161
[Indexed for MEDLINE]
Free PMC Article

CBD: Muscle growth and maturation, DMD

Br J Pharmacol. 2018 Aug 3. doi: 10.1111/bph.14460.

Effects of non-euphoric plant cannabinoids on muscle quality and performance of dystrophic mdx mice.

Iannotti FA[1], Pagano E[2], Moriello AS[1], Alvino FG[3], Sorrentino NC[3], D'Orsi L[3], Gazzerro E[4], Capasso R[5], De Leonibus E[3,6], De Petrocellis L[1], Di Marzo V[1].

Abstract

BACKGROUND AND PURPOSE: Duchenne muscular dystrophy (DMD), caused by dystrophin deficiency, results in chronic inflammation and irreversible skeletal muscle degeneration. Moreover, the associated impairment of autophagy greatly contributes to the aggravation of muscle damage. We explored the possibility of using non-euphoric compounds present in Cannabis sativa, cannabidiol (CBD), cannabidivarin (CBDV) and tetrahydrocannabidivarin (THCV), to reduce inflammation, restore functional autophagy and positively enhance muscle function in vivo. **EXPERIMENTAL APPROACH:** Using quantitative PCR, western blots and $[Ca^{2+}]_i$ measurements, we explored the effects of CBD and CBDV on the differentiation of both murine and human skeletal muscle cells as well as their potential interaction with TRP channels. Male dystrophic mdx mice were injected i.p. with CBD or CBDV at different stages of the disease. After treatment, locomotor tests and biochemical analyses were used to evaluate their effects on inflammation and autophagy. **KEY RESULTS:** CBD and CBDV promoted the differentiation of murine C2C12 myoblast cells into myotubes by increasing $[Ca^{2+}]_i$ mostly via TRPV1 activation, an effect that undergoes rapid desensitization. In primary satellite cells and myoblasts isolated from healthy and/or DMD donors, not only CBD and CBDV but also THCV promoted myotube formation, in this case, mostly via TRPA1 activation. In mdx mice, CBD (60 $mg \cdot kg^{-1}$) and CBDV (60 $mg \cdot kg^{-1}$) prevented the loss of locomotor activity, reduced inflammation and restored autophagy.

CONCLUSION AND IMPLICATIONS: We provide new insights into plant cannabinoid interactions with TRP channels in skeletal muscle, highlighting a potential opportunity for novel co-adjuvant therapies to prevent muscle degeneration in DMD patients.