Cleveland NORML: Medicinal Marijuana Scientific & Medical Evidence Reference

Compiled by Benjamin Morrison for Cleveland NORML as of 7/7/2010

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Aging

CB1 Knockout Mice

Increased mortality, hypoactivity, and hypoalgesia in cannabinoid CB1 receptor knockout mice

Vol. 96, Issue 10, 5780-5785, May 11, 1999
Neurobiology

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Communicated by Tomas Hokfelt, Karolinska Institute, Stockholm, Sweden, March 2, 1999 (received for review December 28, 1998)

Abstract

9-Tetrahydrocannabinol (9-THC), the major psychoactive ingredient in preparations of Cannabis sativa (marijuana, hashish), elicits central nervous system (CNS) responses, including cognitive alterations and euphoria. These responses account for the abuse potential of cannabis, while other effects such as analgesia suggest potential medicinal applications. **To study the role of the major known target of cannabinoids in the CNS, the CB1 cannabinoid receptor, we have produced a mouse strain with a disrupted CB1 gene. CB1 knockout mice appeared healthy and fertile, but they had a significantly increased mortality rate. They also displayed reduced locomotor activity, increased ring catalepsy, and hypoalgesia in hotplate and formalin tests.** 9-THC-induced ring-catalepsy, hypomobility, and hypothermia were completely absent in CB1 mutant mice. In contrast, we still found 9-THC-induced analgesia in the tail-flick test and other behavioral (licking of the abdomen) and physiological (diarrhea) responses after 9-THC administration. Thus, most, but not all, CNS effects of 9-THC are mediated by the CB1 receptor.

Toxicity and Carcinogenicity of Δ9-Tetrahydrocannabinol in Fischer Rats and B6C3F1 Mice

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Received 30 May 1995; accepted 2 October 1995. ; Available online 19 April 2002.

Abstract

Δ9-Tetrahydrocannabinol (Δ9-THC) was studied for potential carcinogenicity in rodents because it is the principal psychoactive ingredient in marihuana and it has potential medicinal uses. Δ9-THC in corn oil was administered by gavage to groups of male and female Fischer rats and B6C3F1 mice at 0, 5, 15, 50, 150, or 500 mg/kg, 5 days a week for 13 weeks and for 13-week plus a 9-week recovery period, and to groups of rats at 0, 12.5, 25, or 50 mg/kg and mice at 0, 125, 250, or 500 mg/kg, 5 times a week for 2 years. In all studies, mean body weights of dosed male and female rats and mice were lower than controls but feed consumptions were similar. Convulsions and hyperactivity were observed in dosed rats and mice; the onset and frequency were dose related. Serum FSH and LH levels in all dosed male rats and corticosterone levels in 25 mg/kg female rats were significantly higher than controls at 15 months in the 2-year studies. Δ9-THC administration for 13 weeks induced testicular atrophy and uterine and ovarian hypoplasia; the lesions persisted in a 9-week recovery period. **In the 2-year studies, survival of dosed rats was higher than controls; that of mice was similar to controls. Incidences of testicular interstitial cell, pancreas and pituitary gland adenomas in male rats, mammary gland fibroadenoma and uterus stromal polyp in female rats, and hepatocellular adenoma/carcinoma in male and female mice were reduced in a dose-related manner.** Decreased tumor incidences may be at least in part due to reduced body weights of dosed animals. Incidences of thyroid gland follicular cell hyperplasia were increased in all dosed groups of male and female mice, and follicular cell adenomas were significantly increased in the 125 mg/kg group of males, but there was no evidence of a dose-related trend in proliferative lesions of the thyroid. There was no evidence that Δ9-THC was carcinogenic in rats or mice.

Autoimmune Diseases

Arthritis

Arthritis and cannabinoids: HU-210 and Win-55,212-2 prevent IL-1α-induced matrix degradation in bovine articular chondrocytes in-vitro

Authors: Mbvundula, Estery C.1; Bunning, Rowena A.D.1; Rainsford, K.D.1
Source: Journal of Pharmacy and Pharmacology, Volume 58, Number 3, March 2006 , pp. 351-358(8)
Publisher: Pharmaceutical Press

Abstract:
Cannabinoids have analgesic, immunomodulatory and anti-inflammatory properties and attenuate joint damage in animal models of arthritis. In this study the mechanisms of action of the synthetic cannabinoid agonists, HU-210 and Win-55,212-2, were studied to determine if they affected interleukin-1 alpha (IL-1α)-induced proteoglycan and collagen degradation in bovine nasal cartilage explant cultures and prostaglandin E2 (PGE2) production in primary cultures of bovine articular chondrocytes. The effects of the inactive enantiomer, Win-55,212-3, were compared with those of the active enantiomer, Win-55,212-2, to determine if the effects were cannabinoid (CB)-receptor mediated. The chondrocytes and explants were stimulated by IL-1α (100 U mL−1 ≡ 0.06 nM and 500 U mL−1 ≡ 0.3 nM, respectively). Proteoglycan breakdown was determined as sulfated glycosaminoglycan (sGAG) release using the dimethylmethylene blue assay. Collagen degradation was determined as hydroxyproline in the conditioned culture media and cartilage digests. PGE2 was determined by ELISA. Expression of cannabinoid receptors, CB1 and CB2; cyclooxygenase-1 and -2 (COX-1 and COX-2); inducible nitric oxide synthase (iNOS); as well as activation of nuclear factor-kappa B (NF-κB) in chondrocytes were studied using immunoblotting techniques and immunofluorescence. The results showed that HU-210 and Win-55,212-2 (5–15 μM) significantly inhibited IL-1-α stimulated proteoglycan ($P < 0.001$) and collagen degradation ($P < 0.001$). Win-55,212-2 (5–10 μM) also significantly inhibited PGE2 production ($P < 0.01$). At 5 μM, Win-55,212-2 inhibited the expression of iNOS and COX-2 and activation of NF-κB. Chondrocytes appeared to constitutively express cannabinoid receptors CB1 and CB2. **It is concluded that biologically stable synthetic cannabinoids protect cartilage matrix from degradation induced by cytokines and this effect is possibly CB-receptor mediated and involves effects on prostaglandin and nitric oxide**

metabolism. Cannabinoids could also be producing these effects via inhibition of NF-κB activation.
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Crohn's Disease

The endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract

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Pages: 944-954
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Abstract:

Numerous investigations have recently demonstrated the important roles of the endocannabinoid system in the gastrointestinal (GI) tract under physiological and pathophysiological conditions. In the GI tract, cannabinoid type 1 (CB1) receptors are present in neurons of the enteric nervous system and in sensory terminals of vagal and spinal neurons, while cannabinoid type 2 receptors are located in immune cells. **Activation of CB1 receptors was shown to modulate several functions in the GI tract, including gastric secretion, gastric emptying and intestinal motility. Under pathophysiological conditions induced experimentally in rodents, the endocannabinoid system conveys protection to the GI tract (e.g. from inflammation and abnormally high gastric and enteric secretions). Such protective activities are largely in agreement with anecdotal reports from folk medicine on the use of Cannabis sativa extracts by subjects suffering from various GI disorders. Thus, the endocannabinoid system may serve as a potentially promising therapeutic target against different GI disorders, including**

frankly inflammatory bowel diseases (e.g. Crohns disease), functional bowel diseases (e.g. irritable bowel syndrome) and secretion- and motility-related disorders. As stimulation of this modulatory system by CB1 receptor agonists can lead to unwanted psychotropic side effects, an alternative and promising avenue for therapeutic applications resides in the treatment with CB1 receptor agonists that are unable to cross the blood–brain barrier, or with compounds that inhibit the degradation of endogenous ligands (endocannabinoids) of CB1 receptors, hence prolonging the activity of the endocannabinoid system.
Keywords Endocannabinoids - Gastrointestinal tract - Sensory neurons - Inflammation

Diabetes

The synthetic cannabinoid HU-210 attenuates neural damage in diabetic mice and hyperglycemic pheochromocytoma PC12 cells

Neurobiology of Disease
Volume 27, Issue 2, August 2007, Pages 174-181

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Available online 24 May 2007.

Abstract:

Diabetic neuropathy (DN) is a common complication of diabetes mellitus resulting in cognitive dysfunction and synaptic plasticity impairment. Hyperglycemia plays a critical role in the development and progression of DN, through a number of mechanisms including increased oxidative stress. Cannabinoids are a diverse family of compounds which can act as antioxidative agents and exhibit neuroprotective properties. We investigated the effect of the synthetic cannabinoid HU-210 on brain function of streptozotocin (STZ)-induced diabetic mice. These animals exhibit hyperglycemia, increased cerebral oxidative stress and impaired brain function. HU-210, through a receptor independent pathway, alleviates the oxidative damage and cognitive

impairment without affecting glycemic control. **To study the neuroprotective mechanism(s) involved, we cultured PC12 cells under hyperglycemic conditions. Hyperglycemia enhanced oxidative stress and cellular injuries were all counteracted by HU-210—in a dose dependent manner. These results suggest cannabinoids might have a therapeutic role in the management of the neurological complications of diabetes.**

Multiple Sclerosis

The endocannabinoid system is dysregulated in multiple sclerosis and in experimental autoimmune encephalomyelitis

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Summary

The ability of cannabinoids to modulate both inflammatory and degenerative neuronal damage prompted investigations on the potential benefits of such compounds in multiple sclerosis (MS) and in animal models of this disorder. Here we measured endocannabinoidlevels, metabolism and binding, and physiological activities in 26 patients with MS (17 females, aged 19–43 years), 25 healthy controls and in mice with experimental autoimmune encephalomyelitis (EAE), a preclinical model of MS. Our results show that MS and EAE are associated with significant alterations of the endocannabinoid system. We found that anandamide (AEA), but not 2-arachidonoylglycerol (2-AG), was increased in the CSF of relapsing MS patients. AEA concentrations were also higher in peripheral lymphocytes of these patients, an effect associated with increased synthesis and reduced degradation of this endocannabinoid. Increased synthesis, reduced degradation, and increased levels of AEA were also detected in the brains of EAE mice in the acute phase of the disease, possibly accounting for its anti-excitotoxicaction in this disorder. Accordingly, neurophysiological recordings from single neurons confirmed that excitatory transmission in EAE slices is inhibited by CB1 receptor activation, while inhibitory transmission is not. **Our study suggests that targeting the endocannabinoid system might be useful for the treatment of MS.**

Key Words: animal models; arachidonic acid; autoimmune encephalitis; excitotoxicity; neuroprotective agents

Abbreviations: AEA, anandamide; 2-AG, 2-arachidonoylglycerol; CB, cannabinoid; CSF, cerebrospinal fluid; EAE, experimental autoimmune encephalomyelitis; ECS, endocannabinoid system; EPSC, excitatory postsynaptic current; FAAH, fatty acid amide hydrolase; HP, holding potential; IPSC, inhibitory postsynaptic current; MS, multiple sclerosis; NAPE-PLD, N-acyl-phosphatidylethanolamines (NAPE)-hydrolysing phospholipase D; PPR, paired pulse ratio

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Addictions

Cocaine

Int J Neuropsychopharmacol. 2008 Apr 1;:1-19. [Publisher]

Enhancement of endocannabinoid neurotransmission through CB1 cannabinoid receptors counteracts the reinforcing and psychostimulant effects of cocaine.

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Cannabinoids, in contrast to typical drugs of abuse, have been shown to exert complex effects on behavioural reinforcement and psychomotor function. **We have shown that cannabinoid agonists lack reinforcing/rewarding properties in the intracranial self-stimulation (ICSS) paradigm and that the CB1 receptor (CB1R) agonist WIN55,212-2 attenuates the reward-facilitating actions of cocaine.** We sought to determine the effects of the endocannabinoid neurotransmission enhancer AM-404 (1, 3, 10, 30 mg/kg) on the changes in ICSS threshold and locomotion elicited by cocaine and extend the study of the effects of WIN55,212-2 (0.3, 1, 3 mg/kg) on cocaine-induced hyperlocomotion. AM-404 did not exhibit reward-facilitating properties, and actually increased self-stimulation threshold at the highest dose. Cocaine significantly reduced self-stimulation threshold, without altering maximal rates of responding. AM-404 (10 mg/kg) attenuated this action of cocaine, an effect which was reversed by pretreatment with the selective CB1R antagonist SR141716A. WIN55,212-2 decreased locomotion at the two highest doses, an effect that was blocked by SR141716A; AM-404 had no effect on locomotion. Cocaine caused a significant, dose-dependent increase in locomotion, which was reduced by WIN55,212-2 and AM-404. SR141716A blocked the effects of WIN55,212-2 and AM-404 on cocaine-induced hyperlocomotion. SR141716A alone had no effect on ICSS threshold or locomotion. **These results indicate that cannabinoids may interfere with brain reward systems responsible for the expression of acute reinforcing/rewarding properties of cocaine, and provide further evidence that the cannabinoid system could be explored as a potential drug discovery target for the treatment of psychostimulant addiction and pathological states associated with psychomotor overexcitability.**

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Aggression

Predatory Aggression

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Cannabis and aggression in animals

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x
Available online 13 October 2004.

The effects of cannabis on aggressive behavior in animals depend on the nature of the aggressive behavior being observed. “Irritable” aggression tends to be increased by cannabis whereas “predatory” and “inter-male” aggression tend to be reduced. If aggressive behavior is examined in these terms, then cannabis is seen to have a differential rather than a dual effect on aggression in animals.

Life Sciences
Volume 11, Issue 3, Part 1, 1 February 1972, Pages 103-111

Abstract
Abstract + References
PDF (334 K)

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Copyright © 1972 Published by Elsevier Science Inc.

Reduction of predatory aggression of rats following administration of delta-9-tetrahydrocannabinol

J. H. McDonough, Jr. , F. J. Manning and T. F. Elsmore
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Received 20 December 1971. Available online 8 November 2002.

Abstract
Twenty rats were individually tested for the occurence of an attack upon a turtle 1, 2, 4, and 8 hours after intraperitoneal injections of either placebo or a 6.4 mg/kg dose of Δ:9-

tetrahydrocannabinol. In comparison to days when the rat received placebo injections, the percentage of attacks at 1 and 2 hours post-injection was significantly less on days when the Δ:9-THC was administered, while at 4 and 8 hours post-injection there was no significant difference between the percentage of attacks on either drug or placebo days. The data support previous research that shows that under certain conditions Δ:9-THC has the effect of reducing aggressive behavior.

Schedule Induced Aggression

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*Chronic Δ9-tetrahydrocannabinol administration and schedule-induced aggression*1, ,*2*

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Received 20 July 1979. Available online 7 November 2002.

Abstract
The effects of 0.5 mg/kg and 1.0 mg/kg of Δ9-tetrahydrocannabinol (Δ9-THC) on key-pecking maintained by a response—initiated fixed interval (FI) schedule of food presentation and schedule-induced aggression in the pigeon were studied. Initially, following the administration of Δ9-THC both the rate of key-pecking and attack responding were markedly reduced. Over sessions, tolerance developed to the suppressant effect on key-pecking, with the rate returning to the predrug level. The suppressing effect of Δ9-THC on the rate of attack remained at or near zero throughout the series of Δ9-THC injections.

Author Keywords: Δ9-tetrahydrocannabinol; Aggressive behavior; Chronic; Schedule-induced

*1 The pyran numbering system for tetrahydrocannabinols was employed. Δ9-tetrahydrocannabinol is equivalent to Δ1-tetrahydrocannabinol using the monoterpenoid numbering system.
*2 This research was supported by USPHS grant MH-98565; manuscript preparation by grant DA-07097 and DA-07130.
Reprints may be obtained from D. R. Cherek, Department of Psychiatry, L.S.U. Medical Center, P.O. Box 33932, , Shreveport, LA 71130, , USA.

Serotonin Levels and Aggression

Pharmacology Biochemistry and Behavior
Volume 7, Issue 2, August 1977, Pages 117-120

Abstract
Abstract + References
PDF (323 K)

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Time course of Δ9-tetrahydrocannabinol inhibition of predatory aggression[*1]

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Received 1 March 1977. Available online 7 November 2002.

Abstract
Three studies assessed the time course of inhibition of predatory aggression and changes in levels of brain serotonin following administration of Δ9-THC. In Study One, six groups of six rats each were administered 1.25 mg/kg Δ9-THC IV and frog-killing behavior was measured at six postinjection intervals: 30, 60, 90, 150, 210, and 270 minutes. In Study Two, four groups of six rats each were tested. Group One received a vehicle control injection and was tested immediately, i.e. zero-minutes, postinjection. The remaining groups received 1.25 mg/kg Δ9-THC, and behavior was measured at 0, 15, and 30 min postinjection. In Study Three, two groups of six rats were treated with the vehicle or 1.25 mg/kg Δ9-THC and sacrificed one minute postinjection. Additional drug groups were sacrificed at 30 and 210 min postinjection. Levels of 5-HT were determined in four brain sections: cortex, midbrain, medulla, and cerebellum. Significant inhibition of predatory aggression was found for groups tested at 0, 15, and 30 min postinjection. Brain levels of 5-HT in the midbrain and/or medulla were significantly increased over the same period.

Author Keywords: Δ9-Tetrahydrocannabinol; Predatory agression; Duration of effect; Serotonin; Midbrain; Medulla

[*1] Synthetic Δ9-THC was obtained by approval of the FDA-NIMH Psychotomimetic Agents Advisory Committee.

Cancer

Breast Cancer

Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells

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Abstract
Invasion and metastasis of aggressive breast cancer cells is the final and fatal step during cancer progression, and is the least understood genetically. Clinically, there are still limited therapeutic interventions for aggressive and metastatic breast cancers available. Clearly, effective and nontoxic therapies are urgently required. Id-1, an inhibitor of basic helix-loop-helix transcription factors, has recently been shown to be a key regulator of the metastatic potential of breast and additional cancers. Using a mouse model, we previously determined that metastatic breast cancer cells became significantly less invasive in vitro and less metastatic in vivo when Id-1 was down-regulated by stable transduction with antisense Id-1. It is not possible at this point, however, to use antisense technology to reduce Id-1 expression in patients with metastatic breast cancer. Here, we report that cannabidiol (CBD), a cannabinoid with a low-toxicity profile, could down-regulate Id-1 expression in aggressive human breast cancer cells. The CBD concentrations effective at inhibiting Id-1 expression correlated with those used to inhibit the proliferative and invasive phenotype of breast cancer cells. CBD was able to inhibit Id-1 expression at the mRNA and protein level in a concentration-dependent fashion. These effects seemed to occur as the result of an inhibition of the Id-1 gene at the promoter level. Importantly, CBD did not inhibit invasiveness in cells that ectopically expressed Id-1. **In conclusion, CBD represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the down-regulation of tumor aggressiveness.** [Mol Cancer Ther 2007;6(11):2921–7]

Breast Cancer
Anticancer Res. 2008 Jan-Feb;28(1A):85-9. [In-Process]

Delta(9)-tetrahydrocannabinol inhibits 17beta-estradiol-induced proliferation and fails to activate androgen and estrogen receptors in MCF7 human breast cancer cells.

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BACKGROUND: Delta(9)-tetrahydrocannabinol (THC) exerts palliative effects in cancer patients, but produces adverse effects on the endocrine and reproductive systems. Experimental evidence concerning such effects is controversial. Whether THC exhibits estrogenic or androgenic activity in vitro was investigated. MATERIALS AND METHODS: Estrogenic effects of THC were analyzed in vitro by measuring the proliferation of estrogen-sensitive MCF7 cells. Androgenic activity was investigated by the A-Screen assay that measures androgen-dependent inhibition of proliferation of the androgen receptor (AR)-positive human mammary carcinoma cell line, MCF7-AR1. **RESULTS:** In contrast to 17beta-estradiol, included as positive control with an EC50 value (concentration required for 50% of maximal 17beta-estradiol-induced proliferation) of 1.00 x 10(-12) M, THC failed to induce cell proliferation in the MCF7 cell line at concentrations between 10(-13) and 10(-4) M. THC inhibited 17beta-estradiol-induced proliferation in wild-type MCF7 and MCF7-AR1 cells, with an IC50 value of 2.6 x 10(-5) M and 9 x 10(-6) M, respectively. **CONCLUSION: THC failed to act as an estrogen, but antagonized 17beta-estradiol-induced proliferation. This effect was independent of the AR expression level.**

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JPET 318:1375-1387, 2006

Chemotherapy, Antibiotics and Gene Therapy

Antitumor Activity of Plant Cannabinoids with Emphasis on the Effect of Cannabidiol on Human Breast Carcinoma

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9-Tetrahydrocannabinol (THC) exhibits antitumor effects on various cancer cell types, but its use in chemotherapy is limited by its psychotropic activity. **We investigated the antitumor activities of other plant cannabinoids, i.e., cannabidiol, cannabigerol,cannabichromene, cannabidiol acid and THC acid, and assessed whether there is any advantage in using Cannabis extracts (enriched in either cannabidiol or THC) over pure cannabinoids. Results obtained in a panel of tumor cell lines clearly indicate that, of the five natural compounds tested, cannabidiol is the most potent inhibitor of cancer cell growth (IC50 between 6.0 and 10.6 μM), with significantly lower potency in noncancer cells.** The cannabidiol-rich extract was equipotent to cannabidiol, whereas cannabigerol and cannabichromene followed in the rank of potency. Both cannabidiol and the cannabidiol-rich extract inhibited the growth of xenograft tumors obtained by s.c. injection into athymic mice of human MDA-MB-231 breast carcinoma or rat v-K-ras-transformed thyroid epithelial cells and reduced lungmetastases deriving from intrapaw injection of MDA-MB-231 cells. Judging from several experiments on its possible cellular and molecular mechanisms of action, we propose that cannabidiol lacks a unique mode of action in the cell lines investigated. **At least for MDA-MB-231 cells, however, our experiments indicate that cannabidiol effect is due to its capability of inducing apoptosis** via: direct or indirect activation of cannabinoid CB2 and vanilloid transient receptor potential vanilloid type-1 receptors and cannabinoid/vanilloid receptor-independent elevation of intracellular Ca2+ and reactive oxygen species. **Our data support the further testing of cannabidiol and cannabidiol-rich extracts for the potential treatment of cancer.**

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Colorectal Cancer

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The cannabinoid 9-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells

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KEYWORDS
colorectal cancer • survival signalling • cannabinoid • apoptosis • BAD

ABSTRACT
Deregulation of cell survival pathways and resistance to apoptosis are widely accepted to be fundamental aspects of tumorigenesis. As in many tumours, the aberrant growth and survival of colorectal tumour cells is dependent upon a small number of highly activated signalling pathways, the inhibition of which elicits potent growth inhibitory or apoptotic responses in tumour cells. Accordingly, there is considerable interest in therapeutics that can modulate survival signalling pathways and target cancer cells for death. There is emerging evidence that cannabinoids, especially 9-tetrahydrocannabinol (THC), may represent novel anticancer agents, due to their ability to regulate signalling pathways critical for cell growth and survival. Here, we report that CB1 and CB2

cannabinoid receptors are expressed in human colorectal adenoma and carcinoma cells, and show for the first time that THC induces apoptosis in colorectal cancer cells. THC-induced apoptosis was rescued by pharmacological blockade of the CB1, but not CB2, cannabinoid receptor. Importantly, THC treatment resulted in CB1-mediated inhibition of both RAS-MAPK/ERK and PI3K-AKT survival signalling cascades; two key cell survival pathways frequently deregulated in colorectal tumours. The inhibition of ERK and AKT activity by THC was accompanied by activation of the proapoptotic BCL-2 family member BAD. Reduction of BAD protein expression by RNA interference rescued colorectal cancer cells from THC-induced apoptosis. **These data suggest an important role for CB1 receptors and BAD in the regulation of apoptosis in colorectal cancer cells. The use of THC, or selective targeting of the CB1 receptor, may represent a novel strategy for colorectal cancer therapy.** © 2007 Wiley-Liss, Inc.

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Glioma

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*Cannabinoids Induce Glioma Stem-like Cell Differentiation and Inhibit Gliomagenesis**

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Glioma stem-like cells constitute one of the potential origins of gliomas, and therefore, their elimination is an essential factor for the development of efficient therapeutic strategies. Cannabinoids are known to exert an antitumoral action on gliomas that relies on at least two mechanisms: induction of apoptosis of transformed cells and inhibition of tumor angiogenesis. However, whether cannabinoids target human glioma stem cells and their potential impact in gliomagenesis are unknown. Here, we show that glioma stem-like cells derived from glioblastoma multiforme biopsies and the glioma cell lines U87MG and U373MG express cannabinoid type 1 (CB1) and type 2 (CB2) receptors and other elements of the endocannabinoid system. In gene array experiments, CB receptor activation altered the expression of genes involved in the regulation of stem

cell proliferation and differentiation. The cannabinoid agonists HU-210 and JWH-133 promoted glial differentiation in a CB receptor-dependent manner as shown by the increased number of S-100- and glial fibrillary acidic protein-expressing cells. In parallel, cannabinoids decreased the cell population expressing the neuroepithelial progenitor marker nestin. Moreover,cannabinoid challenge decreased the efficiency of glioma stem-like cells to initiate glioma formation in vivo, a finding that correlated with decreased neurosphere formation and cell proliferation in secondary xenografts. Gliomas derived from cannabinoid-treated cancer stem-like cells were characterized with a panel of neural markers and evidenced a more differentiated phenotype and a concomitant decrease in nestin expression. **Overall, our results demonstrate that cannabinoids target glioma stem-like cells, promote their differentiation, and inhibit gliomagenesis, thus giving further support to their potential use in the management of malignant gliomas.**

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The on-line version of this article (available at http://www.jbc.org) contains supplemental Figs. 1 and 2 and Table 1.
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Lung Cancer

Original Article
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9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo

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Abstract
9-Tetrahydrocannabinol (THC) is the primary cannabinoid of marijuana and has been shown to either potentiate or inhibit tumor growth, depending on the type of cancer and its pathogenesis. Little is known about the activity of cannabinoids like THC on epidermal growth factor receptor-overexpressing lung cancers, which are often highly aggressive and resistant to chemotherapy. In this study, we characterized the effects of THC on the EGF-induced growth and metastasis of human non-small cell lung cancer using the cell lines A549 and SW-1573 as in vitro models. We found that these cells express the cannabinoid receptors CB1 and CB2, known targets for THC action, and that THC inhibited EGF-induced growth, chemotaxis and chemoinvasion. Moreover, signaling studies indicated that THC may act by inhibiting the EGF-induced phosphorylation of ERK1/2, JNK1/2 and AKT. THC also induced the phosphorylation of focal adhesion kinase at tyrosine 397. Additionally, in in vivo studies in severe combined immunodeficient mice, there was significant inhibition of the subcutaneous tumor growth and lung metastasis of A549 cells in THC-treated animals as compared to vehicle-treated controls. Tumor samples from THC-treated animals revealed antiproliferative and antiangiogenic effects of THC. **Our study suggests that cannabinoids like THC should be explored as novel therapeutic molecules in controlling the growth and metastasis of certain lung cancers.**
Keywords: tetrahydrocannabinol (THC), lung cancer, A549, migration, invasion, EGFR

Lymphoma

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Cannabinoid receptor ligands mediate growth inhibition and cell death in mantle cell lymphoma

Edited by Lukas Huber
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Abstract
We have earlier reported overexpression of the central and peripheral cannabinoid receptors CB1 and CB2 in mantle cell lymphoma (MCL), a B cell non-Hodgkin lymphoma. In this study, treatment with cannabinoid receptor ligands caused a decrease in viability of MCL cells, while control cells lacking CB1 were not affected. Interestingly, equipotent doses of the CB1 antagonist SR141716A and the CB1/CB2 agonist anandamide inflicted additive negative effects on viability. Moreover, treatment with the CB1/CB2 agonist Win-55,212-2 caused a decrease in long-term growth of MCL cells in culture. Induction of apoptosis, as measured by FACS/Annexin V–FITC, contributed to the growth suppressive effect of Win-55,212-2. **Our data suggest that cannabinoid receptors may be considered as potential therapeutic targets in MCL**.

Melanoma

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Cannabinoid receptors as novel targets for the treatment of melanoma

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ABSTRACT
Melanoma causes the greatest number of skin cancer-related deaths worldwide. Despite intensive research, prevention and early detection are the only effective measures against melanoma, so new therapeutic strategies are necessary for the management of this devastating disease. **Here, we evaluated the efficacy of cannabinoid receptor agonists, a new family of potential antitumoral compounds, at skin melanoma. Human melanomas and melanoma cell lines express CB1 and CB2 cannabinoid receptors. Activation of these receptors decreased growth, proliferation, angiogenesis and metastasis, and increased apoptosis, of melanomas in mice.** Cannabinoid antimelanoma activity was independent of the immune status of the animal, could be achieved without overt psychoactive effects and was selective for melanoma cells vs. normal melanocytes. Cannabinoid antiproliferative action on melanoma cells was due, at least in part, to cell cycle arrestat the G1-S transition via inhibition of the prosurvival protein Akt and hypophosphorylation of the pRb retinoblastoma protein tumor suppressor. **These findings may contribute to the design of new chemotherapeutic strategies for the management of melanoma**.—Blázquez,C., Carracedo, A., Barrado, L., Real, P. J., Fernández-Luna, J. L., Velasco, G., Malumbres, M., and Guzmán, M. Cannabinoid receptors as novel targets for the treatment of melanoma.

Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors

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Nonmelanoma skin cancer is one of the most common malignancies in humans. Different therapeutic strategies for the treatment of these tumors are currently being investigated. Given the growth-inhibiting effects of cannabinoids on gliomas and the wide tissue distribution of the two subtypes of cannabinoid receptors (CB1 and CB2), we studied the potential utility of these compounds in anti–skin tumor therapy. Here we show that the CB1 and the CB2 receptor are expressed in normal skin and skin tumors of mice and humans. In cell culture experiments pharmacological activation of cannabinoid receptors induced the apoptotic death of tumorigenic epidermal cells, whereas the viability of nontransformed epidermal cells remained unaffected. Local administration of the mixed CB1/CB2 agonist WIN-55,212-2 or the selective CB2 agonist JWH-133 induced a considerable growth inhibition of malignant tumors generated by inoculation of epidermal tumor cells into nude mice. Cannabinoid-treated tumors showed an increased number of apoptotic cells. This was accompanied by impairment of tumor vascularization, as determined by altered blood vessel morphology and decreased expression of proangiogenic factors (VEGF, placental growth factor, and angiopoietin 2). Abrogation of EGF-R function was also observed in cannabinoid-treated tumors. **These results support a new therapeutic approach for the treatment of skin tumors.**

Cholangiocarcinoma

Cancer Invest. 2010 May;28(4):357-63.
The dual effects of delta(9)-tetrahydrocannabinol on cholangiocarcinoma cells: anti-invasion activity at low concentration and apoptosis induction at high concentration.
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Abstract
Currently, only gemcitabine plus platinum demonstrates the considerable activity for cholangiocarcinoma. The anticancer effect of Delta (9)-tetrahydrocannabinol (THC), the principal active component of cannabinoids has been demonstrated in various kinds of cancers. We therefore evaluate the antitumor effects of THC on cholangiocarcinoma cells. Both cholangiocarcinoma cell lines and surgical specimens from cholangiocarcinoma patients expressed cannabinoid receptors. **THC inhibited cell proliferation, migration and invasion, and induced cell apoptosis. THC also decreased actin polymerization and reduced tumor cell survival in anoikis assay. pMEK1/2 and pAkt demonstrated the lower extent than untreated cells.**

Consequently, THC is potentially used to retard cholangiocarcinoma cell growth and metastasis.
PMID: 19916793 [PubMed - indexed for MEDLINE]

Metastasis

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9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo

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Abstract
9-Tetrahydrocannabinol (THC) is the primary cannabinoid of marijuana and has been shown to either potentiate or inhibit tumor growth, depending on the type of cancer and its pathogenesis. Little is known about the activity of cannabinoids like THC on epidermal growth factor receptor-overexpressing lung cancers, which are often highly aggressive and resistant to chemotherapy. In this study, we characterized the effects of THC on the EGF-induced growth and metastasis of human non-small cell lung cancer using the cell lines A549 and SW-1573 as in vitro models. We found that these cells express the cannabinoid receptors CB1 and CB2, known targets for THC action, and that THC inhibited EGF-induced growth, chemotaxis and chemoinvasion. Moreover, signaling studies indicated that THC may act by inhibiting the EGF-induced phosphorylation of ERK1/2, JNK1/2 and AKT. THC also induced the phosphorylation of focal adhesion kinase at tyrosine 397. Additionally, in in vivo studies in severe combined immunodeficient mice, there was significant inhibition of the subcutaneous tumor growth and lung metastasis of A549 cells in THC-treated animals as compared to vehicle-treated controls. Tumor samples from THC-treated animals revealed antiproliferative and antiangiogenic effects of THC. **Our study suggests that cannabinoids like THC should be explored as novel therapeutic molecules in controlling the growth and metastasis of certain lung cancers.**
Keywords: tetrahydrocannabinol (THC), lung cancer, A549, migration, invasion, EGFR

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Endocannabinoids as emerging suppressors of angiogenesis and tumor invasion (Review)

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Abstract
The medicinal properties of extracts from the hemp plant Cannabis sativa have been known for centuries but only in the 90s membrane receptors for the Cannabis major principle were discovered in mammalian cells. Later on the endogenous ligands for the cannabinoid receptors were identified and the term 'endocannabinoid system' was coined to indicate the complex signaling system of cannabinoid receptors, endogenous ligands and the enzymes responsible for their biosynthesis and inactivation. The 'endocannabinoid system' is involved in a broad range of functions and in a growing number of pathological conditions. There is increasing evidence that endocannabinoids are able to inhibit cancer cell growth in culture as well as in animal models. Most work has focused on the role of endocannabinoids in regulating tumor cell growth and apoptosis and ongoing research is addressed to further dissect the precise mechanisms of cannabinoid antitumor action. **However, endocannabinoids are now emerging as suppressors of angiogenesis and tumor spreading since they have been reported to inhibit angiogenesis, cell migration and metastasis in different types of cancer, pointing to a potential role of the endocannabinoid system as a target for a therapeutic approach of such malignant diseases. The potential use of cannabinoids to retard tumor growth and spreading is even more appealing considering that they show a good safety profile, regarding toxicity, and are already used in cancer patients as palliatives to stimulate appetite and to prevent devastating effects such as nausea, vomiting and pain.**

Experimental Cell Research
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Research Article

Anandamide inhibits adhesion and migration of breast cancer cells

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Abstract
The endocannabinoid system regulates cell proliferation in human breast cancer cells. We reasoned that stimulation of cannabinoid CB1 receptors could induce a non-invasive phenotype in breast mtastatic cells. In a model of metastatic spreading in vivo, the metabolically stable anandamide analogue, 2-methyl-2′-F-anandamide (Met-F-AEA), significantly reduced the number and dimension of metastatic nodes, this effect being antagonized by the selective CB1 antagonist SR141716A. In MDA-MB-231 cells, a highly invasive human breast cancer cell line, and in TSA-E1 cells, a murine breast cancer cell line, Met-F-AEA inhibited adhesion and migration on type IV collagen in vitro without modifying integrin expression: both these effects were antagonized by SR141716A. In order to understand the molecular mechanism involved in these processes, we analyzed the phosphorylation of FAK and Src, two tyrosine kinases involved in migration and adhesion. In Met-F-AEA-treated cells, we observed a decreased tyrosine phosphorylation of both FAK and Src, this effect being attenuated by SR141716A. **We propose that CB1 receptor agonists inhibit tumor cell invasion and metastasis by modulating FAK phosphorylation, and that CB1receptor activation might represent a novel therapeutic strategy to slow down the growth of breast carcinoma and to inhibit its metastatic diffusion in vivo.**

Keywords: Endocannabinoid; Cancer; Metastasis

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Anandamide is an endogenous inhibitor for the migration of tumor cells and T lymphocytes

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Received: 26 September 2003 Accepted: 27 January 2004 Published online: 18 March 2004
Abstract Cell migration is of paramount importance in physiological processes such as immune surveillance, but also in the pathological processes of tumor cell migration and metastasis development. The factors that regulate this tumor cell migration, most prominently neurotransmitters, have thus been the focus of intense investigation. While the majority of neurotransmitters have a stimulatory effect on cell migration, we herein report the inhibitory effect of the endogenous substance anandamide on both tumor cell and lymphocyte migration. Using a collagen-based three-dimensional migration assay and time-lapse videomicroscopy, we have observed that the anandamide-mediated signals for CD8+ T lymphocytes and SW 480 colon carcinoma cells are each mediated by distinct cannabinoid receptors (CB-Rs). Using the specific agonist docosatetraenoylethanolamide (DEA), we have observed that the norepinephrine-induced migration of colon carcinoma cells is inhibited by the CB1-R. The SDF-1–induced migration of CD8+T lymphocytes was, however, inhibited via the CB2-R, as shown by using the specific agonist JWH 133. **Therefore, specific inhibition of tumor cell migration via CB1-R engagement might be a selective tool to prevent**

metastasis formation without depreciatory effects on the immune system of cancer patients.

Keywords Anandamide - Cannabinoid receptors - Cell migration - T lymphocytes - Tumor cells

The FASEB Journal Express Article doi:10.1096/fj.02-1129fje
Published online July 3, 2003

Inhibitory effects of cannabinoid CB1 receptor stimulation on tumor growth and metastatic spreading: actions on signals involved in angiogenesis and metastasis

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Stimulation of cannabinoid CB1 receptors by 2-methyl-arachidonyl-2′-fluoro-ethylamide (Met-F-AEA) inhibits the growth of a rat thyroid cancer cell-derived tumor in athymic mice by inhibiting the activity of the oncogene product p21ras. Here we report that Met-F-AEA also blocks the growth of tumors previously induced in nude mice by the s.c. injection of the same rat thyroid carcinoma cells. Met-F-AEA significantly inhibited, in tumors as well as transformed cells, the expression of the vascular endothelial growth factor, an angiogenetic factor known to be up-regulated by p21ras, as well as of one of its receptors, flt-1/VEGFR-1. The levels of the cyclin-dependent kinase inhibitor p27(kip1), which is down-regulated by p21ras, were instead increased by Met-F-AEA. All these effects were antagonized by the selective CB1 receptor antagonist SR141716A. Met-F-AEA inhibited in vitro the growth of a metastasis-derived thyroid cancer cell line more potently than a primary cancer cell line. Therefore, the hypothesis that CB1 receptor stimulation interferes not only with angiogenesis but also with metastatic processes was tested in a widely used model of metastatic infiltration in vivo, the Lewis lung carcinoma (3LL) in C57Bl/6 mice. Three weeks from the paw injection of 3LL cells, Met-F-AEA reduced significantly the number of metastatic nodes, in a way antagonized by SR141716A. **Our findings indicate that CB1 receptor agonists might be used therapeutically to retard tumor growth in vivo by inhibiting at once tumor growth, angiogenesis, and metastasis.**

Key words: thyroid • cancer • endocannabinoid • p27 • lung • VEGF

Prostate Cancer

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Priority Reports

Cannabinoid Receptor as a Novel Target for the Treatment of Prostate Cancer

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Cannabinoids, the active components of Cannabis sativa Linnaeus (marijuana) and their derivatives have received renewed interest in recent years due to their diverse pharmacologic activities such as cell growth inhibition, anti-inflammatory effects and tumor regression. Here we show that expression levels of both cannabinoid receptors, CB1 and CB2, are significantly higher in CA-human papillomavirus-10 (virally transformed cells derived from adenocarcinoma of human prostate tissue), and other human prostate cells LNCaP, DUI45, PC3, and CWR22R1 than in human prostate epithelial and PZ-HPV-7 (virally transformed cells derived from normal human prostate tissue) cells. WIN-55,212-2 (mixed CB1/CB2 agonist) treatment with androgen-responsive LNCaP cells resulted in a dose- (1-10 μmol/L) and time-dependent (24-48 hours) inhibition of cell growth, blocking of CB1 and CB2 receptors by their antagonists SR141716 (CB1) and SR144528 (CB2) significantly prevented this effect. Extending this observation, we found that WIN-55,212-2 treatment with LNCaP resulted in a dose- (1-10 μmol/L) and time-dependent (24-72 hours) induction of apoptosis (a), decrease in protein and mRNA expression of androgen receptor (b), decrease in intracellular protein and mRNA expression of prostate-specific antigen (c), decrease in secreted prostate-specific antigen levels (d), and decrease in protein expression of proliferation cell nuclear antigen and vascular endothelial growth factor (e). **Our results suggest that WIN-55,212-2 or other non–habit-forming cannabinoid receptor agonists could be developed as novel therapeutic agents for the treatment of prostate cancer**.
Key Words: Cannabinoid • WIN-55,212-2 • PSA • AR

Prostate. 2003 Jun 15;56(1):1-12.

Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production.

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Abstract
BACKGROUND: Anandamide (ANA) is an endogenous lipid which acts as a cannabinoid receptor ligand and with potent anticarcinogenic activity in several cancer cell types. METHODS: The inhibitory effect of ANA on the epidermal growth factor receptor (EGFR) levels expressed on the EGF-stimulated prostatic cancer cells LNCaP, DU145, and PC3 was estimated by ELISA tests. The anti-proliferative and cytotoxic effects of ANA were also evaluated on these human prostatic cancer cell lines by growth tests, flow cytometric analyses, trypan blue dye exclusion assays combined with the Papanicolaou cytological staining method. RESULTS: ANA induced a decrease of EGFR levels on LNCaP, DU145, and PC3 prostatic cancer cells by acting through cannabinoid CB(1) receptor subtype and this leaded to an inhibition of the EGF-stimulated growth of these cells. Moreover, the G(1) arrest of metastatic DU145 and PC3 growth was accompanied by a massive cell death by apoptosis and/or necrosis while LNCaP cells were less sensitive to cytotoxic effects of ANA. The apoptotic/necrotic responses induced by ANA on these prostatic cancer cells were also potentiated by the acidic ceramidase inhibitor, N-oleoylethanolamine and partially inhibited by the specific ceramide synthetase inhibitor, fumonisin B1 indicating that these cytotoxic actions of ANA might be induced via the cellular ceramide production. **CONCLUSIONS: The potent anti-proliferative and cytotoxic effects of ANA on metastatic prostatic cancer cells might provide basis for the design of new therapeutic agents for effective treatment of recurrent and invasive prostatic cancers.** Copyright 2003 Wiley-Liss, Inc.
PMID: 12746841 [PubMed - indexed for MEDLINE]

Oral Cancer

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Cannabinoids Inhibit Cellular Respiration of Human Oral Cancer Cells.

Whyte DA, Al-Hammadi S, Balhaj G, Brown OM, Penefsky HS, Souid AK.
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Abstract
Background and Purpose: The primary cannabinoids, Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and Delta(8)-tetrahydrocannabinol (Delta(8)-THC) are known to disturb the mitochondrial function and possess antitumor activities. These observations prompted us to investigate their effects on the mitochondrial O(2) consumption in human oral cancer cells (Tu183). This epithelial cell line overexpresses bcl-2 and is highly resistant to anticancer drugs. Experimental Approach: A phosphorescence analyzer that measures the time-dependence of O(2) concentration in cellular or mitochondrial suspensions was used for this purpose. Key Results: A rapid decline in the rate of respiration was observed when Delta(9)-THC or Delta(8)-THC was added to the cells. The inhibition was concentration-dependent, and Delta(9)-THC was the more potent of the two compounds. Anandamide (an endocannabinoid) was ineffective; suggesting the effects of Delta(9)-THC and Delta(8)-THC were not mediated by the cannabinoidreceptors. Inhibition of O(2) consumption by cyanide confirmed the oxidations occurred in the mitochondrial respiratory chain. **Delta(9)-THC inhibited the respiration of isolated mitochondria from beef heart. Conclusions and Implications: These results show the cannabinoids are potent inhibitors of Tu183 cellular respiration and are toxic to this highly malignant tumor.** Copyright © 2010 S. Karger AG, Basel.
PMID: 20516734 [PubMed - as supplied by publisher]

Pancreatic Cancer

Cannabinoids Induce Apoptosis of Pancreatic Tumor Cells via Endoplasmic Reticulum Stress–Related Genes

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Abstract
Pancreatic adenocarcinomas are among the most malignant forms of cancer and, therefore, it is of especial interest to set new strategies aimed at improving the prognostic of this deadly disease. The present study was undertaken to investigate the action of cannabinoids, a new family of potential antitumoral agents, in pancreatic cancer. We show that cannabinoid receptors are expressed in human pancreatic tumor cell lines and tumor biopsies at much higher levels than in normal pancreatic tissue. Studies conducted with MiaPaCa2 and Panc1 cell lines showed that cannabinoid administration (a) induced apoptosis, (b) increased ceramide levels, and (c) up-regulated mRNA levels of the stress protein p8. These effects were prevented by blockade of the CB2 cannabinoid receptor or by pharmacologic inhibition of ceramide synthesis de novo. Knockdown experiments using selective small interfering RNAs showed the involvement of p8 via its downstream endoplasmic reticulum stress–related targets activating transcription factor 4 (ATF-4) and TRB3 in Δ9-tetrahydrocannabinol–induced apoptosis. **Cannabinoids also reduced the growth of tumor cells in two animal models of pancreatic cancer. In addition, cannabinoid treatment inhibited the spreading of pancreatic tumor cells. Moreover, cannabinoid administration selectively increased apoptosis and TRB3 expression in pancreatic tumor cells but not in normal tissue.** In conclusion, results presented here show that cannabinoids lead to apoptosis of pancreatic tumor cells via a CB2 receptor and de novo synthesized ceramide-dependent up-r**egulation of p8 and the endoplasmic reticulum stress–related genes ATF-4 and TRB3. These findings may contribute to set the basis for a new therapeutic approach for the treatment of pancreatic cancer.** (Cancer Res 2006; 66(13): 6748-55)

Cardiovascular Disease

Artherosclerosis

Letters to Nature

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There is a Corrigendum (26 May 2005) associated with this document.

Low dose oral cannabinoid therapy reduces progression of atherosclerosis in mice

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Atherosclerosis is a chronic inflammatory disease, and is the primary cause of heart disease and stroke in Western countries1. Derivatives of cannabinoids such as delta-9-tetrahydrocannabinol (THC) modulate immune functions2 and therefore have potential for the treatment of inflammatory diseases. We investigated the effects of THC in a murine model of established atherosclerosis. Oral administration of THC (1 mg kg-1 per day) resulted in significant inhibition of disease progression. This effective dose is lower than the dose usually associated with psychotropic effects of THC. Furthermore, we detected the CB2 receptor (the main cannabinoid receptor expressed on immune cells2, 3) in both human and mouse atherosclerotic plaques. Lymphoid cells isolated from THC-treated mice showed diminished proliferation capacity and decreased interferon- secretion. Macrophage chemotaxis, which is a crucial step for the development of atherosclerosis1, was also inhibited in vitro by THC. All these effects were completely blocked by a specific CB2 receptor antagonist4. **Our data**

demonstrate that oral treatment with a low dose of THC inhibits atherosclerosis progression in the apolipoprotein E knockout mouse model, through pleiotropic immunomodulatory effects on lymphoid and myeloid cells. Thus, THC or cannabinoids with activity at the CB2 receptor may be valuable targets for treating atherosclerosis.

Myocardial Infarct

Subject Category: Review Article
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Endocannabinoids and cannabinoid receptors in ischaemia–reperfusion injury and preconditioning

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Top

Abstract
Ischaemia–reperfusion (I/R) is a pivotal mechanism of organ injury during stroke, myocardial infarction, organ transplantation and vascular surgeries. Ischaemic preconditioning (IPC) is a potent endogenous form of tissue protection against I/R injury. On the one hand, endocannabinoids have been implicated in the protective effects of IPC through cannabinoid CB1/CB2 receptor-dependent and -independent mechanisms. However, there is evidence suggesting that endocannabinoids are overproduced during various forms of I/R, such as myocardial infarction or whole body I/R associated with circulatory shock, and may contribute to the cardiovascular depressive state associated with these pathologies. Previous studies using synthetic CB1 receptor agonists or knockout mice demonstrated CB1 receptor-dependent protection against cerebral I/R injury in various animal models. In contrast, several follow-up reports have shown protection afforded by CB1 receptor antagonists, but not agonists. Excitedly, emerging studies using potent CB2 receptor agonists and/or knockout mice have provided compelling evidence that CB2 receptor activation is protective against myocardial, cerebral and hepatic I/R injuries by decreasing the endothelial cell activation/inflammatory response (for example, expression of adhesion molecules, secretion of chemokines, and so on), and by attenuating the leukocyte chemotaxis, rolling, adhesion to endothelium, activation and transendothelial migration, and

interrelated oxidative/nitrosative damage. **This review is aimed to discuss the role of endocannabinoids and CB receptors in various forms of I/R injury (myocardial, cerebral, hepatic and circulatory shock) and preconditioning, and to delineate the evidence supporting the therapeutic utility of selective CB2 receptor agonists, which are devoid of psychoactive effects, as a promising new approach to limit I/R-induced tissue damage.**

Gastrointestinal Disorders

GERDS Gastro-intestinal Reflux Syndrome

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LEADING ARTICLE

Endocannabinoid overactivity and intestinal inflammation

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Cannabinoid receptors of type 1 and 2 (CB1 and CB2), endogenous ligands that activate them (endocannabinoids), and mechanisms for endocannabinoid biosynthesis and inactivation have been identified in the gastrointestinal system. Activation of CB1 receptors by endocannabinoids produces relaxation of the lower oesophageal sphincter and inhibition of gastric acid secretion, intestinal motility, and fluid stimulated secretion. However, stimulation of cannabinoid receptors impacts on

gastrointestinal functions in several other ways. **Recent data indicate that the endocannabinoid system in the small intestine and colon becomes over stimulated during inflammation in both animal models and human inflammatory disorders. The pathological significance of this "endocannabinoid overactivity" and its possible exploitation for therapeutic purposes are discussed here.**

Abbreviations: 2-AG, 2-arachidonoylglycerol; CB1 and CB2, cannabinoid receptors of type 1 and 2; DNBS, dinitrobenzene sulphonic acid; FAAH, fatty acid amide hydrolase; IBD, inflammatory bowel diseases; LPS, lipopolysaccharide; TNF-, tumour necrosis factor ; TRPV1, transient receptor potential vanilloid type 1 channel

Ulcers

Cannabinoid CB1-mediated inhibition of stress-induced gastric ulcers in rats

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Abstract

The effect of cannabinoid drugs (i.p.) on cold/restraint stress-induced gastric ulcers was studied in rats. The cannabinoid receptor agonist (WIN 55,212-2, 0.1-1 mg/kg), but not the less active isomer WIN 55,212-3 (1 mg/kg), reduced gastric ulceration. The protective effect of WIN 55,212-2 (1 mg/kg) was counteracted by the cannabinoid CB1 receptor antagonist SR141716A, but not by the cannabinoid CB2 receptor antagonist SR144528. **These results indicate that the antiulcer effect of the cannabinoid receptor agonist WIN 55,212-2 is mediated by cannabinoid CB1 receptors.**

Musculo-Skeletal Disorders

Osteopathic Manipulation

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ORIGINAL CONTRIBUTION

Cannabimimetic Effects of Osteopathic Manipulative Treatment

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Endogenous cannabinoids activate cannabinoid receptors in the brain and elicit mood-altering effects. Parallel effects (eg,anxiolysis, analgesia, sedation) may be elicited by osteopathic manipulative treatment (OMT), and previous research has shownthat the endorphin system is not responsible for OMT's mood-altering effects. The authors investigate whether OMT generated cannabimimetic effects for 31 healthy subjects in a dual-blind, randomized controlled trial that measured changes in subjects' scores on the 67-item Drug Reaction Scale (DRS). Chemical ionization gas chromatography and mass spectrometry were also used to determine changes in serum levels of anandamide (AEA), 2-arachidonoylglycerol (2-AG), and oleylethanolamide (OEA). In subjects

receiving OMT, posttreatment DRS scores increased significantly for the cannabimimetic descriptors good, high, hungry, light-headed, and stoned, with significant score decreases for the descriptors inhibited, sober, and uncomfortable.Mean posttreatment AEA levels (8.01 pmol/mL) increased 168% over pretreatment levels (2.99 pmol/mL), mean OEA levels decreased 27%, and no changes occurred in 2-AG levels in the group receiving OMT. Subjects in the sham manipulative treatment group recorded mixed DRS responses, with both increases and decreases in scores for cannabimimetic and noncannabimimetic descriptors and no changes in sera levels. When changes in serum AEA were correlated with changes in subjects' DRS scores, increased AEA correlated best with an increase for the descriptors cold and rational, and decreased sensations for the descriptors bad, paranoid, and warm. **The authors propose that healing modalities popularly associated with changes in the endorphin system, such as OMT, may actually be mediated by the endocannabinoid system.**

Osteoporosis

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MEDICAL SCIENCES

Peripheral cannabinoid receptor, CB2, regulates bone mass

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Edited by Hector F. DeLuca, University of Wisconsin, Madison, WI, and approved November 11, 2005 (received for review May 22, 2005)

Abstract
The endogenous cannabinoids bind to and activate two G protein-coupled receptors, the predominantly central cannabinoid receptor type 1 (CB1) and peripheral cannabinoid receptor type 2 (CB2). Whereas CB1 mediates the cannabinoid psychotropic, analgesic, and orectic effects, CB2 has been implicated recently in the regulation of liver fibrosis and atherosclerosis. Here we show that CB2-deficient mice have a markedly accelerated age-related trabecular bone loss and cortical expansion,

although cortical thickness remains unaltered. These changes are reminiscent of human osteoporosis and may result from differential regulation of trabecular and cortical bone remodeling. The CB2–/– phenotype is also characterized by increased activity of trabecular osteoblasts (bone-forming cells), increased osteoclast (the bone-resorbing cell) number, and a markedly decreased number of diaphyseal osteoblast precursors. CB2 is expressed in osteoblasts, osteocytes, and osteoclasts. A CB2-specific agonist that does not have any psychotropic effects enhances endocortical osteoblast number and activity and restrains trabecular osteoclastogenesis, apparently by inhibiting proliferation of osteoclast precursors and receptor activator of NF-B ligand expression in bone marrow-derived osteoblasts/stromal cells. The same agonist attenuates ovariectomy-induced bone loss and markedly stimulates cortical thickness through the respective suppression of osteoclast number and stimulation of endocortical bone formation. **These results demonstrate that the endocannabinoid system is essential for the maintenance of normal bone mass by osteoblastic and osteoclastic CB2 signaling. Hence, CB2 offers a molecular target for the diagnosis and treatment of osteoporosis, the most prevalent degenerative disease in developed countries.**

bone remodeling | HU-308 | osteoblast | osteoclast

The endogenous cannabinoids bind to and activate the cannabinoid receptors 1 and 2 (CB1 and CB2, respectively). Both are seven-transmembrane domain receptors, and they share 44% identity. They are coupled to the inhibitory guanine nucleotide-binding regulatory protein subclass of G proteins and inhibit stimulated adenylyl cyclase activity (1). That CB1 and CB2 are not functionally identical is demonstrated by the selective regulation of ion channels by only CB1 (2). CB1 is present in the brain and in peripheral neurons and accounts for most of the actions of cannabinoid drugs and endocannabinoids on the central nervous system (3, 4). CB2 was reported in the immune system (5), in liver cirrhosis (6), and in atherosclerotic plaques (7).
In vertebrates, bone mass and shape are determined by continuous remodeling consisting of the concerted and balanced action of osteoclasts, the bone-resorbing cells, and osteoblasts, the bone-forming cells. Osteoporosis, the most prevalent degenerative disease in developed countries, results from the impairment of this balance, leading to bone loss and increased fracture risk. It has been recently reported that bone remodeling is subject to central control through pathways that involve signaling by the hypothalamic receptors for leptin and neuropeptide Y (8, 9), which are also associated with the regulation of endocannabinoid brain levels (10). These observations led us to assess the role of the endocannabinoid signaling system in the regulation of bone mass. Indeed, we demonstrate here a low bone mass phenotype in mice deficient for the peripheral cannabinoid receptor (CB2), which is normally expressed in osteoblasts, osteoclasts, and their precursors. A CB2-specific agonist, which has no psychotropic or other central effects, regulates the activity of these

cells and attenuates ovariectomy (OVX)-induced bone loss. These data suggest an important regulatory role of the endocannabinoid system in bone and offer molecular targets for the development of diagnostic and therapeutic approaches to osteoporosis.

Neurological Effects & Disorders

Neurogenesis (Growth of Neurons)

Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis

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Abstract (provisional)

Background
Adult neurogenesis is a particular example of brain plasticity that is partially modulated by the endocannabinoid system. Whereas the impact of synthetic cannabinoids on the neuronal progenitor cells has been described, there has been lack of information about the action of plant-derived extracts on neurogenesis. Therefore we here focused on the effects of delta-9-tetrahydrocannabinol (THC) and Cannabidiol (CBD) fed to female C57Bl/6 and Nestin-GFP-reporter mice on proliferation and maturation of neuronal progenitor cells and spatial learning performance. In addition we used cannabinoid receptor 1 (CB1) deficient mice and treatment with CB1 antagonist AM251 in Nestin-GFP-reporter mice to investigate the role of the CB1 receptor in adult neurogenesis in detail.
Results
THC and CBD differed in their effects on spatial learning and adult neurogenesis. CBD did not impair learning but increased adult neurogenesis, whereas THC reduced learning without affecting adult neurogenesis. We found the neurogenic effect of CBD to be dependent on the CB1 receptor, which is expressed over the whole dentate gyrus. Similarly, the neurogenic effect of environmental enrichment and voluntary wheel running depends on the presence of the CB1 receptor. We found that in the absence of CB1 receptors, cell proliferation was increased and neuronal differentiation reduced, which could be related to CB1 receptor mediated signaling in Doublecortin (DCX)-expressing intermediate progenitor cells.
Conclusion
CB1 affected the stages of adult neurogenesis that involve intermediate highly proliferative progenitor cells and the survival and maturation of new neurons. The pro-

neurogenic effects of CBD might explain some of the positive therapeutic features of CBD-based compounds.

ALS

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Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mice

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ABSTRACT

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by the selective loss of motoneurons in the spinal cord, brain stem, and motor cortex. However, despite intensive research, an effective treatment for this disease remains elusive. In this study we show that treatment of postsymptomatic, 90-day-old SOD1G93A mice with a synthetic cannabinoid, WIN55,212–2, significantly delays disease progression. Furthermore, genetic ablation of the Faah enzyme, which results in raised levels of the endocannabinoid anandamide, prevented the appearance of disease signs in 90-day-old SOD1G93A mice. Surprisingly, elevation of cannabinoid levels with either WIN55,212–2 or Faah ablation had no effect on life span. Ablation of the CB1 receptor, in contrast, had no effect on disease onset inSOD1G93A mice but significantly extended life span. **Together these results show that cannabinoids have significant neuroprotective effects in this model of ALS and suggest that these beneficial effects may be mediated by non-CB1 receptor mechanisms**.—

Bilsland, L. G., Dick, J. R. T., Pryce, G., Petrosino, S., DiMarzo, V., Baker, D., Greensmith, L. Increasing cannabinoid levels by pharmacological and genetic manipulation delay disease progression in SOD1 mice.

Alzheimer's Disease

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A Molecular Link between the Active Component of Marijuana and Alzheimer's Disease Pathology

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Abstract:
Alzheimer's disease is the leading cause of dementia among the elderly, and with the ever-increasing size of this population, cases of Alzheimer's disease are expected to triple over the next 50 years. Consequently, the development of treatments that slow or halt the disease progression have become imperative to both improve the quality of life for patients and reduce the health care costs attributable to Alzheimer's disease. Here, we demonstrate that the active component of marijuana, 9-tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid -peptide (A) aggregation, the key pathological marker of Alzheimer's disease. Computational modeling of the THC-AChE interaction revealed that THC binds in the peripheral anionic site of AChE, the critical region involved in amyloidgenesis. **Compared to currently approved drugs prescribed for the treatment of Alzheimer's disease, THC is a considerably superior inhibitor of A aggregation, and this study provides a previously unrecognized molecular mechanism through which cannabinoid molecules may directly impact the progression of this debilitating disease**.

Epilepsy

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Activation of the Cannabinoid Type-1 Receptor Mediates the Anticonvulsant Properties of Cannabinoids in the Hippocampal Neuronal Culture Models of Acquired Epilepsy and Status Epilepticus

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Abstract:
Cannabinoids have been shown to have anticonvulsant properties, but no studies have evaluated the effects of cannabinoids in the hippocampal neuronal culture models of acquired epilepsy (AE) and status epilepticus (SE). This study investigated the anticonvulsant properties of the cannabinoid receptor agonist R(+)-[2,3-dihydro-5-methyl-3-[(morpholinyl)methyl]pyrrolol[1,2,3 de]-1,4-benzoxazinyl]-(1-naphthalenyl)methanone (WIN 55,212-2)in primary hippocampal neuronal culture models of both AE and SE. WIN 55,212-2 produced dose-dependent anticonvulsant effects against both spontaneous recurrent epileptiform discharges (SRED) (EC50 = 0.85 μM) and SE (EC50 = 1.51 μM), with total suppression of seizure activity at 3 μM and of SE activity at 5 μM. The anticonvulsant properties of WIN 55,212-2 in these preparations were both stereospecific and blocked by the cannabinoid type-1 (CB1) receptor antagonist N-(piperidin-1-yl-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamidehydrochloride (SR141716A; 1 μM), showing a CB1 receptor-dependent pathway. The inhibitory effect of WIN 55,212-2 against low Mg2+-induced SE is the first observation in this model of total suppression of SE by a selective pharmacological agent. The clinically used anticonvulsants phenytoin and phenobarbital were not able to abolish low Mg2+-induced SE at concentrations up to 150 μM. The results from this study show CB1 receptor-mediated anticonvulsant effects of the cannabimimetic WIN 55,212-2 against both SRED and low Mg2+-induced SE in primary

hippocampal neuronal cultures and show that these in vitro models of AE and SE may represent powerful tools to investigate the molecular mechanisms mediating the effects of cannabinoids on neuronal excitability.

Since the isolation and purification of the psychotropically active constituent 9-tetrahydrocannabinol from Cannabis in the 1960s (reviewed in Mechoulam, 2000), a number of studies have shown the anticonvulsant effects of cannabinoids in a variety of experimentally induced seizure models that include maximal electroshock-induced convulsions, electrical kindling, chemoconvulsants, and audiogenic and photogenic seizures (Corcoran et al., 1973; Karler et al., 1974; Wada et al., 1975; Consroe and Wolkin, 1977; Chiu et al., 1979; Wallace et al., 2001, 2002; Shafaroodi et al., 2004). In addition, several reports have been published on the clinical use of cannabinoids as antiepileptic agents in humans (reviewed in Consroe, 1998). Thus, it is important to elucidate the molecular mechanisms mediating the anticonvulsanteffects of cannabinoids.
A major advance in the field of cannabinoid research came with the discovery and cloning of receptor proteins that bind cannabinoids with high affinity (reviewed in Mechoulam, 2000). Within the central nervous system, the Gi/o protein-coupled cannabinoid type-1 (CB1) receptor is widely distributed and is the primary mediator of the physiological and psychotropic effects of cannabinoids in the brain (Devane et al., 1988; Matsuda et al., 1990; Herkenham et al., 1991; Howlett, 1995). In recent years, a better understanding of the endocannabinoid system has led to the development of highly specific synthetic compounds that have been instrumental in the pharmacological evaluation of cannabinoid receptor-mediated regulation of synaptic transmission (Howlett et al., 2004). Utilizing the maximal electroshock (MES)-induced seizure model, studies from this laboratory provided the first evidence that both cannabinoid and endocannabinoid compounds produced anticonvulsant effects through activation of the CB1 receptor (Wallace et al., 2001, 2002). Additionally, the active cannabimimetic compound WIN 55,212-2 was shown to totally suppress spontaneous recurrent epileptiform discharges (SRED; seizures) via CB1 receptor activation in the rat pilocarpine model of acquired epilepsy (AE) (Wallace et al., 2003). This study further showed that endocannabinoids,acting through the CB1 receptor, were essential for maintaining tonic inhibition of seizure frequency and duration in this in vivo model of AE (Wallace et al., 2003). Although these in vivo models of acute seizure and AE are useful for studying the anticonvulsant effects of CB1 receptor activation on intact systems (Wallace et al., 2001, 2002, 2003), they are limited in their ability to carry out sophisticated molecular techniques needed to study underlying cellular mechanisms. Thus, it is important to utilize well established in vitro neuronal preparations that are more amenable to sophisticated electrophysiological and molecular biological procedures to evaluate the cellular mechanisms underlying the anticonvulsant properties of cannabinoids. The hippocampal neuronal culture (HNC) model of AE is a well established model that exhibits SRED for the life of the neurons in culture

(Sombati and DeLorenzo, 1995) and has been shown by our laboratory and others to manifest many of the electrophysiological and molecular properties of intact animal models of AE (Kim and Rhim, 2004; Delorenzo et al., 2005). It is also important to evaluate the anticonvulsant effects of cannabinoids against continuous seizure activity, status epilepticus (SE), a major neurological emergency that is often resistant to conventional anticonvulsant treatments (Delorenzo et al., 2005). The well established HNC model of SE (Sombati and DeLorenzo, 1995) has been widely used to evaluate the effects of SE on neuronal cell physiology and molecular changes (Pal et al., 1999; Blair et al., 2004; Mangan and Kapur, 2004; Delorenzo et al., 2005). Thus, the HNC models of AE and SE may serve as valuable tools for elucidating the cellular mechanisms underlying the anticonvulsant properties of cannabinoids because these in vitro models are amenable to experimental manipulation and allow for direct analysis of neurons undergoing SRED and SE in culture (Sombati and DeLorenzo, 1995; Churn et al., 2000; Blair et al., 2004; Delorenzo et al., 2005).
In the current study, we set out to investigate the effects of the cannabimimetic WIN 55,212-2 on seizure activity in the in vitro HNC models of AE and SE (Sombati and DeLorenzo, 1995). Whole-cell current-clamp (WCC) analysis was utilized to directly evaluate the effect of WIN 55,212-2 on SRED and SE and to determine whether a CB1 receptor-dependent pathway was involved. The results show that WIN 55,212-2 was effective in terminating SRED and SE in a stereoselective manner. **In addition, these anticonvulsant effects of WIN 55,212-2 were mediated through activation of the CB1 receptor. This study shows that the HNC models of AE and SE provide powerful tools to further elucidate the cellular mechanisms underlying the effect of cannabinoids on seizure activity and neuronal excitability.**

Huntington's Disease

Neurobiology of Disease
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Severe deficiency of the fatty acid amide hydrolase (FAAH) activity segregates with the Huntington's disease mutation in peripheral lymphocytes

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Abstract
The search for peripheral markers of neurodegenerative diseases aims at identifying molecules that could help in monitoring the effects of future therapeutics in easily accessible cells. Here we focused on the involvement of the endocannabinoid system in Huntington's disease (HD). We assayed peripheral lymphocytes from HD patients and healthy controls, and found that the activity of the fatty acid amide hydrolase (FAAH), the enzyme that degrades the endocannabinoid anandamide (AEA), was dramatically decreased (down to less than 10%) in HD compared to healthy subjects. Concomitantly, the endogenous levels of AEA were 6-fold higher in HD versus healthy lymphocytes, while the other elements of the endocannabinoid system were not affected by HD. Low FAAH activity in HD lymphocytes was not due to down-regulation of protein expression, but rather to blockage of enzyme activity by a cytosolic and irreversible inhibitor. Finally, pre-HD patients showed defective FAAH activity, as did the brain of HD patients compared with healthy controls. Taken together, our data indicate that FAAH activity in lymphocytes mirrors some of the metabolic changes which take place in the brain, it is a measurable non-genetic peripheral marker that segregates with the HD mutation, and it might serve as a target to test chemicals active on the widespread toxic effects of the mutant protein.

Keywords: Endocannabinoid; Enzyme inhibition; FAAH; Huntington's disease; Lymphocyte

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Abstract
Full Text + Links
PDF (339 K)

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Symptom-related changes of endocannabinoid and palmitoylethanolamide levels in brain areas of R6/2 mice, a transgenic model of Huntington's disease

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Abstract
Previous studies have shown an impairment of the endocannabinoid system in experimental models of Huntington's disease. In transgenic R6/2 mice, created by inserting exon 1 of the human IT15 mutant gene into the mouse, and exhibiting 150 CAG repeats as well as signs of HD, a progressive decline of CB1 receptor expression and an abnormal sensitivity to CB1 receptor stimulation have been reported. Here, by using isotope-dilution liquid chromatography–mass spectrometry, we investigated whether the levels of three endogenous neuroprotective substances, the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and palmitoylethanolamide (PEA), are altered in different brain areas of transgenic R6/2 versus wild-type (WT) mice at two different disease phases, i.e. in pre-symptomatic (4.5 weeks) or overtly symptomatic (10 weeks) R6/2 mice versus age-matched WT mice (n = 4/group). Except for a 25% decrease in 2-AG levels in the cortex, no significant changes in endocannabinoid and PEA levels were observed in pre-symptomatic R6/2 versus WT mice. By contrast, in symptomatic R6/2 mice the levels of all three compounds were significantly (30–60%) decreased in the striatum, whereas little changes were observed in the hippocampus, and a 28% decrease of 2-AG levels, accompanied by a 50% increase of AEA levels, was found in the cortex. **These findings show that endocannabinoid levels change in a disease phase- and region-specific way in the brain of R6/2 mice and indicate that an impaired endocannabinoid system is a hallmark of symptomatic HD, thus suggesting that**

drugs inhibiting endocannabinoid degradation might be used to treat this disease.

Keywords: Cannabinoid; Anandamide; 2-Arachidonoylglycerol; CB1 receptor; Basal ganglia; Locomotion; Cortex

Tourette's

Clinical Research

Neuropsychopharmacology (2003) 28, 384-388.
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Treatment of Tourette Syndrome with Delta-9-Tetrahydrocannabinol (9-THC): No Influence on Neuropsychological Performance

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ABSTRACT

Previous studies provide evidence that marijuana (Cannabis sativa) and delta-9-tetrahydrocannabinol (9-THC), the major psychoactive ingredient of marijuana, respectively, are effective in the treatment of tics and behavioral problems in Tourette syndrome (TS). It, therefore, has been speculated that the central cannabinoid receptor system might be involved in TS pathology. However, in healthy marijuana users there is an ongoing debate as to whether the use of cannabis causes acute and/or long-term cognitive deficits. In this randomized double-blind placebo-controlled study, we investigated the effect of a treatment with up to 10 mg 9-THC over a 6-week period on neuropsychological performance in 24 patients suffering from TS. **During medication and immediately as well as 5-6 weeks after withdrawal of 9-THC treatment, no detrimental effect was seen on learning curve, interference, recall and recognition of word lists, immediate visual memory span, and divided attention. Measuring immediate verbal memory span, we even found a trend towards a significant improvement during and after treatment. Results from this study corroborate previous data suggesting that in patients suffering from TS, treatment with 9-THC causes neither acute nor long-term cognitive deficits.** Larger and longer-duration controlled studies are recommended to provide more information on the adverse effect profile of THC in patients suffering from TS.

Mental Disorders

General Psychosis

Are cannabis use disorders associated with an earlier age at onset of psychosis? A study in first episode schizophrenia.

Sevy S, Robinson DG, Napolitano B, Patel RC, Gunduz-Bruce H, Miller R, McCormack J, Lorell BS, Kane J.
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Abstract
INTRODUCTION: The purpose of this study is to determine if an earlier age at onset of positive symptoms in schizophrenia is associated with cannabis use disorders (CUD). METHODS: 49 first-episode schizophrenia subjects with CUD were compared to 51 first-episode schizophrenia subjects with no substance use disorders for demographic and clinical variables. A multivariate logistic regression was performed to determine the joint relationship between variables significantly associated with CUD on univariate

testing and ascertain if these variables independently predict CUD. Significance level was set at p<0.05. RESULTS: 74% of CUD subjects had the onset of CUD before the onset of positive symptoms. Compared to non-substance abusing subjects, CUD subjects were predominantly male, younger at study entry, had an earlier age at onset of positive symptoms, less educational attainment, a lower self-socioeconomic status, better premorbid childhood social adjustment, a trend for poorer premorbid childhood academic adjustment, less motor abnormalities but more severe hallucinations and delusions. In the multivariate analysis, only male gender, worse socio-economic status, better premorbid childhood social adjustment, and more severe positive symptoms at study entry were associated with a lifetime history of CUD. **DISCUSSION: Although cannabis use precedes the onset of illness in most patients, there was no significant association between onset of illness and CUD that was not accounted for by demographic and clinical variables. Previous studies implicating CUD in the onset of schizophrenia may need to more comprehensively assess the relationship between CUD and schizophrenia, and take into account additional variables that we found associated with CUD. Copyright © 2010 Elsevier B.V. All rights reserved.**

Bipolar Disorder

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Cannabinoids in bipolar affective disorder: a review and discussion of their therapeutic potential

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Bipolar affective disorder is often poorly controlled by prescribed drugs. Cannabis use is common in patients with this disorder and anecdotal reports suggest that some patients take it to alleviate symptoms of both mania and depression. We undertook a literature review of cannabis use by patients with bipolar disorder and of the neuropharmacological properties of cannabinoids suggesting possible therapeutic effects in this condition. No systematic studies of cannabinoids in bipolar disorder were found to exist, although some patients claim that cannabisrelieves symptoms of mania and/or depression. **The cannabinoids 9-tetrahydrocannabinol (THC) and cannabidiol (CBD) may exert sedative, hypnotic, anxiolytic, antidepressant, antipsychotic and anticonvulsant effects.** Pure synthetic cannabinoids, such as

dronabinol and nabilone and specific plant extracts containing THC, CBD, or amixture of the two in known concentrations, are available and can be delivered sublingually. **Controlled trials of these cannabinoids as adjunctive medication in bipolar disorder are now indicated.**

Depression

Local enhancement of cannabinoid CB1 receptor signalling in the dorsal hippocampus elicits an antidepressant-like effect.

ORIGINAL ARTICLES
Behavioural Pharmacology. 18(5-6):431-438, September 2007.
McLaughlin, Ryan J.; Hill, Matthew N.; Morrish, Anna C.; Gorzalka, Boris B.
Abstract:
Systemic administration of direct cannabinoid CB1 receptor agonists and inhibitors of the hydrolytic enzyme fatty acid amide hydrolase have been shown to elicit antidepressant effects. Moreover, the endocannabinoid system in the hippocampus is sensitive to both chronic stress and antidepressant administration, suggesting a potential role of this system in emotional changes associated with these regimens. The aim of this study was to determine if cannabinoid CB1 receptors in the hippocampus modulate emotionality in rats as assessed via the forced swim test. Male Sprague-Dawley rats were bilaterally implanted with cannulae directed at the dentate gyrus of the dorsal hippocampus and subsequently received three infusions of either the cannabinoid CB1 receptor agonist HU-210 (1 and 2.5 [mu]g), the fatty acid amide hydrolase inhibitor URB597 (0.5 and 1 [mu]g), the cannabinoid CB1 receptor antagonist AM251 (1 and 2.5 [mu]g), or vehicle (dimethyl sulfoxide) and were assessed in the forced swim test. Infusion of both doses of HU-210 resulted in a dramatic reduction in immobility and increase in swimming behaviour, indicative of an antidepressant response, which was partially reversed by coadministration of AM251. No effect of URB597 administration or any effect following the administration of AM251 alone was, however, observed. **These data indicate that activation of CB1 receptors in the dentate gyrus of the hippocampus results in an antidepressant-like response. Collectively, these data highlight the potential importance of changes in the hippocampal endocannabinoid system following stress or antidepressant treatment with respect to the manifestation and/or treatment of depression.**
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Electroconvulsive shock treatment differentially modulates cortical and subcortical endocannabinoid activity

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: 2-AG, 2-arachidonylglycerol; AEA, anandamide; ECS, electroconvulsive shock; FAAH, fatty acid amide hydrolase, PFC, prefrontal cortex.

Abstract:
Previous studies indicate that the endocannabinoid system is a potential target for the treatment of depression. To further examine this question we assessed the effects of electroconvulsive shock (ECS) treatment, both a single session and 10 daily sessions, on endocannabinoid content, CB1 receptor binding parameters and CB1 receptor-mediated [35S]GTPγS binding in the prefrontal cortex, hippocampus, hypothalamus and amygdala. A single ECS session resulted in a general reduction in the binding affinity of the CB1 receptor in all brain regions examined, as well as reductions in N-arachidonylethanolamine (anandamide) content in the prefrontal cortex and the hippocampus, reduced hydrolysis of anandamide by fatty acid amide hydrolase (FAAH) in the prefrontal cortex and an increase in the binding site density of the CB1 receptor in the amygdala. Following 10 ECS sessions, all these effects subsided except for the reductions in anandamide content in the prefrontal cortex, which increased in magnitude, as well as the reductions in FAAH activity in the prefrontal cortex. Additionally, repeated ECS treatment resulted in a significant reduction in the binding site density of the CB1 receptor in the prefrontal cortex, but did not alter CB1 receptor-mediated [35S]GTPγS binding. Repeated ECS treatment also significantly enhanced the sensitivity of CB1receptor-mediated [35S]GTPγS binding in the amygdala. **Collectively, these data demonstrate that ECS treatment results in a down-regulation of cortical and an up-regulation of subcortical endocannabinoid activity, illustrating the possibility that the role of the endocannabinoid system in affective illness may be both complex and regionally specific.**

Volume 62, Issue 10, 15 November 2007, Pages 1103-1110
Stress and Anxiety: Developmental and Therapeutic Perspectives

Antidepressant-like Activity of the Fatty Acid Amide Hydrolase Inhibitor URB597 in a Rat Model of Chronic Mild Stress

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Background
The endocannabinoid anandamide may be involved in the regulation of emotional reactivity. In particular, it has been shown that pharmacological inhibition of the enzyme fatty acid amide hydrolase (FAAH), which catalyzes the intracellular hydrolysis of anandamide, elicits anxiolytic-like and antidepressant-like effects in rodents.
Methods
We investigated the impact of chronic treatment with the selective FAAH inhibitor, URB597 (also termed KDS-4103), on the outcomes of the chronic mild stress (CMS) in rats, a behavioral model with high isomorphism to human depression.

Results
Daily administration of URB597 (.3 mg·kg−1, intraperitoneal [IP]) for 5 weeks corrected the reduction in body weight gain and sucrose intake induced by CMS. The antidepressant imipramine (20 mg·kg−1, once daily, IP) produced a similar response, whereas lower doses of URB597 were either marginally effective (.1 mg·kg−1) or ineffective (.03 mg·kg−1). Treatment with URB597 (.3 mg·kg−1) resulted in a profound inhibition of brain FAAH activity in both CMS-exposed and control rats. Furthermore, the drug regimen increased anandamide levels in midbrain, striatum, and thalamus.

Conclusions
URB597 exerts antidepressant-like effects in a highly specific and predictive animal model of depression. These effects may depend on the ability of URB597 to enhance anandamide signaling in select regions of the brain.

Schizophrenia

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SummaryPlus
Full Text + Links
PDF (348 K)

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Short communication

Cannabinoid CB1 receptor antagonism markedly increases dopamine receptor-mediated stereotypies

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Received 31 August 2006; revised 18 December 2006; accepted 8 January 2007.
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Abstract
The contribution of the endocannabinoid system to dopamine-mediated disorganized behavior in schizophrenia is discussed. We used a model of concurrent stimulation of dopamine D1 and D2receptors to evaluate the role of this system in dopamine-mediated stereotypies measured in a hole-board test. Pretreatment with the cannabinoid CB1 receptor antagonist N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichloro-phenyl)-4-methyl-1H-pyrazole-3-carboxamide (SR141716A; 1 mg/kg) potentiated stereotyped behavior induced by coadministration of the dopamine D1receptor agonist SKF 38393 (0.05, 0.1 and 1 mg/kg) and the dopamine D2 receptor agonist quinpirole (0.25 mg/kg). **Thus, the endocannabinoid system acts as a brake for abnormal behavior associated with dopaminergic overactivation.**

Schizophrenia Research
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Acute effects of Δ9-tetrahydrocannabinol and standardized cannabis extract on the auditory evoked mismatch negativity

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Abstract
Reduced amplitudes of auditory evoked mismatch negativity (MMN) have often been found in schizophrenic patients, indicating deficient auditory information processing and working memory. Cannabis-induced psychotic states may resemble schizophrenia. Currently, there are discussions focusing on the close relationship between cannabis, the endocannabinoid and dopaminergic system, and the onset of schizophrenic psychosis. This study investigated the effects of cannabis on MMN amplitude in 22 healthy volunteers (age 28 ± 6 years, 11 male) by comparing Δ9-tetrahydrocannabinol (Δ9-THC) and standardized cannabis extract containing Δ9-THC and cannabidiol (CBD) in a prospective, double-blind, placebo-controlled cross-over design. The MMNs resulting from 1000 auditory stimuli were recorded by 32 channel EEG. The standard stimuli were 1000 Hz, 80 dB SPL, and 100 ms duration. The deviant stimuli differed in frequency (1500 Hz). Significantly greater MMN amplitude values at central electrodes were found under cannabis extract, but not under Δ9-THC. There were no significant differences between MMN amplitudes at frontal electrodes. MMN amplitudes at central electrodes were significantly correlated with 11-OH-THC concentration, the most important psychoactive metabolite of Δ9-THC. **Since the main difference between Δ9-THC and standardized cannabis extract is CBD, which seems to have neuroprotective and anti-psychotic properties, it can be speculated whether the greater MMN amplitude that may imply higher cortical activation and cognitive performance is related to the positive effects of CBD.** This effect may be relevant for auditory cortex activity in particular because only MMN amplitudes at the central, but not at the frontal electrodes were enhanced under cannabis.

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Anandamide levels in cerebrospinal fluid of first-episode schizophrenic patients: Impact of cannabis use

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Received 17 February 2007; revised 6 April 2007; accepted 25 April 2007. Available online 13 June 2007.

Abstract
Background
Previous studies have shown that cerebrospinal fluid (CSF) from schizophrenic patients contains significantly higher levels of the endogenous cannabinoid anandamide than does CSF from healthy volunteers. Moreover, CSF anandamide levels correlated inversely with psychotic symptoms, suggesting that anandamide release in the central nervous system (CNS) may serve as an adaptive mechanism countering neurotransmitter abnormalities in acute psychoses. In the present study we examined whether cannabis use may alter such a mechanism.
Methods
We used liquid chromatography/mass spectrometry (LC/MS) to measure anandamide levels in serum and CSF from first-episode, antipsychotic-naïve schizophrenics (n = 47) and healthy volunteers (n = 81). Based on reported patterns of cannabis use and urine Δ9-tetrahydrocannabinol (Δ9-THC) tests, each subject group was further divided into two subgroups: 'low-frequency' and 'high-frequency' cannabis users (lifetime use ≤ 5 times and > 20 times, respectively). Serum Δ9-THC was investigated to determine acute use and three patients were excluded from the analysis due to detectable Δ9-THC levels in serum.

Results
Schizophrenic low-frequency cannabis users (n = 25) exhibited > 10-fold higher CSF anandamide levels than did schizophrenic high-frequency users (n = 19, p = 0.008), healthy low-frequency (n = 55, p < 0.001) or high-frequency users (n = 26, p < 0.001). In contrast, no significant differences in serum anandamide levels were found among the four subgroups. CSF anandamide levels and disease symptoms were negatively correlated in both user groups.
Conclusions
The results indicate that frequent cannabis exposure may down-regulate anandamide signaling in the CNS of schizophrenic patients, but not of healthy individuals. Thus, our findings suggest that alterations in endocannabinoid signaling might be an important component of the mechanism through which cannabis impacts mental health.

Stress and Anxiety

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Cannabinoids: Interactions with other drugs

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Review
Endocannabinoid system and stress and anxiety responses
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Received 28 June 2004; revised 11 December 2004; accepted 16 January 2005.
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Abstract
Cannabinoid agonists induce complex and often contradictory effects on anxiety in humans and experimental animals. The data from animal tests provide evidence of dose-dependent bidirectional modulation of anxiety by the cannabinoid system and the importance of environmental context. The mechanisms mediating the effects of cannabinoids on anxiety-related responses appear to involve CB1 and non-

CB1 cannabinoid receptors. In addition, the CRH, GABAA, cholecystokinin, opioid and serotonergic systems have also been implicated. Brain regions such as the amygdala, hippocampus and cortex, directly involved in the regulation of emotional behavior, contain high densities of CB1 receptors. Mutant mice lacking CB1 receptors show anxiogenic-like and depressive-like phenotypes in several tests, as well as profound alterations in their adrenocortical activity. Pharmacological blockade of CB1 receptors induces anxiety in rats, and inhibition of anandamide metabolism produces anxiolytic-like effects. **Thus, the endocannabinoid system appears to play a pivotal role in the regulation of emotional states and may constitute a novel pharmacological target for anti-anxiety therapy.**

Pain

Arthritic Pain

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The antinociceptive effect of Δ9-tetrahydrocannabinol in the arthritic rat involves the CB2 cannabinoid receptor

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Received 11 August 2006; revised 10 May 2007; accepted 15 May 2007. Available online 5 June 2007.

Abstract
Cannabinoid CB2 receptors have been implicated in antinociception in animal models of both acute and chronic pain. We evaluated the role both cannabinoid CB1 and CB2 receptors in mechanonociception in non-arthritic and arthritic rats. The antinociceptive effect of Δ9-tetrahydrocannabinol (Δ9THC) was determined in rats following administration of the cannabinoid CB1 receptor-selective antagonist, SR141716A, the cannabinoid CB2 receptor-selective antagonist, SR144528, or vehicle. Male Sprague–Dawley rats were rendered arthritic using Freund's complete adjuvant and tested for mechanical hyperalgesia in the paw-pressure test. Arthritic rats had a

baseline paw-pressure of 83 ± 3.6g versus a paw-pressure of 177 ± 6.42g in non-arthritic rats. SR144528 or SR141716A (various doses mg/kg; i.p.) or 1:1:18 (ethanol:emulphor:saline) vehicle were injected 1 h prior to Δ9THC (4mg/kg; i.p) or 1:1:18 vehicle and antinociception determined 30min post Δ9THC. AD50's for both antagonists were calculated with 95% confidence limits. In addition, midbrain and spinal cord were removed for determination of cannabinoid CB1 and CB2 receptor protein density in the rats. SR144528 significantly attenuated the antinociceptive effect of Δ9THC in the arthritic rats [AD50 = 3.3 (2.7–4) mg/kg], but not in the non-arthritic rats at a dose of 10/mg/kg. SR141716A significantly attenuated Δ9THC-induced antinociception in both the non-arthritic [AD50 = 1.4 (0.8–2) mg/kg] and arthritic rat [AD50= 2.6 (1.8–3.1) mg/kg]. SR141716A or **SR144528 alone did not result in a hyperalgesic effect as compared to vehicle. Our results indicate that the cannabinoid CB2 receptor plays a critical role in cannabinoid-mediated antinociception, particularly in models of chronic inflammatory pain.**

Fibromyalgia

Delta-9-THC based monotherapy in fibromyalgia patients on experimentally induced pain, axon reflex flare, and pain relief

Authors: Schley, Marcus1; Legler, Andreas1; Skopp, Gisela2; Schmelz, Martin1; Konrad, Christoph1; Rukwied, Roman1
Source: Current Medical Research and Opinion, Volume 22, Number 7, July 2006 , pp. 1269-1276(8)
Publisher: LibraPharm

Abstract:
Objective: Fibromyalgia (FM) is a chronic pain syndrome characterized by a distinct mechanical hyperalgesia and chronic pain. Recently, cannabinoids have been demonstrated as providing anti-nociceptive and anti-hyperalgesic effects in animal and human studies. Here, we explored in nine FM patients the efficacy of orally administered delta-9-tetrahydrocannabinol (THC) on electrically induced pain, axon reflex flare, and psychometric variables.
Research design and methods: Patients received a daily dose of 2.5-15 mg of delta-9-THC, with a weekly increase of 2.5 mg, as long as no side effects were reported. Psychometric variables were assessed each week by means of the West Haven-Yale Multidimensional Pain Inventory (MPI), Pittsburgh Sleep Quality Index (PSQI), Medical outcome survey-short form (MOS SF-36), the Pain Disability Index (PDI), and the Fibromyalgia Impact Questionnaire (FIQ). In addition, patients recorded daily, in a diary, their overall pain intensity on a numeric scale. Each week, pain and axon reflex flare was evoked experimentally by administration of high intensity constant current pulses (1

Hz, pulse width 0.2 ms, current increase stepwise from 2.5-12.5 mA every 3 minutes) delivered via small surface electrodes, attached to the volar forearm skin.
Main outcome measures: Daily pain recordings by the patient, experimentally induced pain, and axon reflex flare recorded by a laser Doppler scanner.
Results: Five of nine FM patients withdrew during the study due to adverse side effects. Delta-9-THC had no effect on the axon reflex flare, whereas electrically induced pain was significantly attenuated after doses of 10-15 mg delta-9-THC ($p < 0.05$). Daily-recorded pain of the FM patients was significantly reduced ($p < 0.01$).
Conclusions: **This pilot study demonstrated that a generalized statement that delta-9-THC is an analgetic drug cannot be made. However, a sub-population of FM patients reported significant benefit from the delta-9-THC monotherapy. The unaffected electrically induced axon reflex flare, but decreased pain perception, suggests a central mode of action of the cannabinoid.**

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DOI: 10.1185/030079906X112651
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The Journal of Pain
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Nabilone for the Treatment of Pain in Fibromyalgia

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Received 19 April 2007; revised 27 August 2007; accepted 26 September 2007.
Available online 5 November 2007.

Abstract
A randomized, double-blind, placebo-controlled trial was conducted to determine the benefit of nabilone in pain management and quality of life improvement in 40 patients with fibromyalgia. After a baseline assessment, subjects were titrated up on nabilone, from 0.5 mg PO at bedtime to 1 mg BID over 4 weeks or received a corresponding placebo. At the 2- and 4-week visits, the primary outcome measure, visual analog scale (VAS) for pain, and the secondary outcome measures, number of tender points, the average tender point pain threshold, and the Fibromyalgia Impact Questionnaire (FIQ), were evaluated. After a 4-week washout period, subjects returned for reassessment of the outcome measures. There were no significant differences in population

demographics between groups at baseline. There were significant decreases in the VAS (–2.04, P< .02), FIQ (–12.07, P < .02), and anxiety (–1.67, P < .02) in the nabilone treated group at 4 weeks. There were no significant improvements in the placebo group. The treatment group experienced more side effects per person at 2 and 4 weeks (1.58, P < .02 and 1.54, P < .05), respectively. Nabilone appears to be a beneficial, well-tolerated treatment option for fibromyalgia patients, with significant benefits in pain relief and functional improvement.

Perspective

To our knowledge, this is the first randomized, controlled trial to assess the benefit of nabilone, a synthetic cannabinoid, on pain reduction and quality of life improvement in patients with fibromyalgia. As nabilone improved symptoms and was well-tolerated, it may be a useful adjunct for pain management in fibromyalgia.

Inflammatory and Neuropathic Pain

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Cannabis in painful HIV-associated sensory neuropathy
A randomized placebo-controlled trial

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Objective: To determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model.
Methods: Prospective randomized placebo-controlled trial conducted in the inpatient General Clinical Research Center between May 2003 and May 2005 involving adults with painful HIV-associated sensory neuropathy. Patients were randomly assigned to smoke either cannabis (3.56% tetrahydrocannabinol) or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Primary outcome measures included ratings of chronic pain and the percentage achieving >30% reduction in pain intensity. Acute analgesic and anti-hyperalgesic effects of smoked cannabis were

assessed using a cutaneous heat stimulation procedure and the heat/capsaicin sensitization model.
Results: Fifty patients completed the entire trial. Smoked cannabis reduced daily pain by 34% (median reduction; IQR = –71, –16) vs 17% (IQR = –29, 8) with placebo (p = 0.03). **Greater than 30% reduction in pain was reported by 52% in the cannabis group and by 24% in the placebo group** (p = 0.04). The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo (p < 0.001). Cannabis reduced experimentally induced hyperalgesia to both brush and von Frey hair stimuli (p 0.05) but appeared to have little effect on the painfulness of noxious heat stimulation. **No serious adverse events were reported.**
Conclusion: Smoked cannabis was well tolerated and effectively relieved chronic neuropathic pain from HIV-associated sensory neuropathy. The findings are comparable to oral drugs used for chronic neuropathic pain.

Subject Category: Review Article
British Journal of Pharmacology advance online publication 12 November 2007; doi: 10.1038/sj.bjp.0707531

Cannabinoid CB2 receptors: a therapeutic target for the treatment of inflammatory and neuropathic pain

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Received 24 July 2007; Revised 24 September 2007; Accepted 4 October 2007; Published online 12 November 2007.

Abstract
Cannabinoids suppress behavioural responses to noxious stimulation and suppress nociceptive transmission through activation of CB1 and CB2receptor subtypes. CB1 receptors are expressed at high levels in the central nervous system (CNS), whereas CB2 receptors are found predominantly, but not exclusively, outside the CNS. CB2 receptors are also upregulated in the CNS and dorsal root ganglia by pathological pain states. Here, we review behavioural, neurochemical and electrophysiological data, which identify cannabinoid CB2 receptors as a therapeutic target for treating pathological pain states with limited centrally, mediated side effects. The development of CB2-selective agonists (with minimal affinity for CB1) as well as mutant mice lacking CB2 receptors has provided pharmacological and genetic tools required to evaluate the effectiveness of CB2 agonists in suppressing persistent pain states. This review will examine the efficacy of cannabinoid CB2-selective agonists in suppressing acute,

inflammatory and neuropathic nociception following systemic and local routes of administration. **Data derived from behavioural, neurochemical and neurophysiological approaches are discussed to better understand the relationship between antinociceptive effects induced by CB2-selective agonists in behavioural studies and neural mechanisms of pain suppression. Finally, the therapeutic potential and possible limitations of CB2-based pharmacotherapies for pathological pain states induced by tissue and nerve injury are discussed.**

Migraines

Neuropsychopharmacology (2007) 32, 1384–1390. doi:10.1038/sj.npp.1301246; published online 22 November 2006

Endocannabinoids in Chronic Migraine: CSF Findings Suggest a System Failure

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Received 13 June 2006; Revised 7 August 2006; Accepted 14 August 2006; Published online 22 November 2006.

Abstract:
Based on experimental evidence of the antinociceptive action of endocannabinoids and their role in the modulation of trigeminovascular system activation, we hypothesized that the endocannabinoid system may be dysfunctional in chronic migraine (CM). We examined whether the concentrations of N-arachidonoylethanolamide (anandamide, AEA), palmitoylethanolamide (PEA), and 2-arachidonoylglycerol (2-AG) in the CSF of patients with CM and with probable CM and probable analgesic-overuse headache (PCM+PAOH) are altered compared with control subjects. The above endocannabinoids were measured by high-performance liquid chromatography (HPLC), and quantified by isotope dilution gas-chromatography/mass-spectrometry. Calcitonin gene-related peptide (CGRP) levels were also determined by RIA method and the end products of nitric oxide (NO), the nitrites, by HPLC. CSF concentrations of AEA were significantly lower and those of PEA slightly but significantly higher both in patients with CM and

PCM+PAOH than in nonmigraineur controls ($p<0.01$ and $p<0.02$, respectively). A negative correlation was found between AEA and CGRP levels in CM and PCM+PAOH patients ($r=0.59$, $p<0.01$ and $r=-0.65$, $p<0.007$; respectively). A similar trend was observed between this endocannabinoid and nitrite levels. **Reduced levels of AEA in the CSF of CM and PCM+PAOH patients may reflect an impairment of the endocannabinoid system in these patients, which may contribute to chronic head pain and seem to be related to increased CGRP and NO production. These findings support the potential role of the cannabinoid (CB)1 receptor as a possible therapeutic target in CM.**

Pain Processing

Clinical and Experimental Pharmacology and Physiology
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Clinical and Experimental Pharmacology and Physiology 34 (5-6), 439–449.
doi:10.1111/j.1440-1681.2007.04592.x

CB1 RECEPTOR ACTIVATION IN THE BASOLATERAL AMYGDALA PRODUCES ANTINOCICEPTION IN ANIMAL MODELS OF ACUTE AND TONIC NOCICEPTION

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Summary:
1.
Recent studies have suggested that the basolateral nucleus of the amygdala (BLA) participates in the processing of pain information, especially noxious somatic information. Cannabinoid receptors or CB1 mRNA are expressed more in the BLA than in other nuclei of the amygdala. Thus, the aim of the present study was to examine

whether CB1 receptors in the BLA may be involved in modulating acute and/or tonic nociceptive processing.
2.
Adult rats were exposed to intra-BLA microinjection of the cannabinoid receptor agonist (R)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl) pyrrolo [1,2,3,-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone mesylate [WIN 55,212-2 (1, 2.5, 5 or 10 μg/side)] and subjected to the tail flick and formalin tests.
3.
The rats demonstrated a dose-dependent increase in latency to withdraw from a thermal noxious stimulus in the tail flick test and a decrease in formalin-induced pain behaviours. The antinociceptive effects of the CB1 receptor agonist WIN 55,212-2 (10 μg/side) in both tests were attenuated in the presence of the selective CB1 receptor antagonist, N-(piperidin-1-yl)-5-(4-iodophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole-3- carboxamide (AM251; 0.55 ng/side). Administration of the CB1 receptor antagonist AM251 (0.55, 5.5, or 55.5 ng/side) alone did not alter the nociceptive thresholds in either test. Bilateral microinjection of the selective CB2 receptor antagonist N-[(1S)-endo-1,3,3-trimethyl bicyclo [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide (SR144528; 1 μg/side) had no effect on the antinociception produced by WIN 55,212-2, suggesting that the antinociceptive actions of WIN 55,212-2 are mediated by CB1 receptors.
4.
The findings suggest the existence of a CB1-mediated inhibitory system in the BLA that, when activated, can diminish responsivity to acute and tonic noxious stimuli, but that normally has no tonic effect on the response

Pre-emptive antinociceptin

European Journal of Pharmacology
Volume 568, Issues 1-3, 30 July 2007, Pages 173-176

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Short communication

Pre-emptive antinociceptive effects of a synthetic cannabinoid in a model of neuropathic pain

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Received 5 March 2007; revised 21 April 2007; accepted 24 April 2007. Available online 22 May 2007.

Abstract
The antinociceptive effects of WIN55,212-2, a synthetic cannabinoid, were evaluated in the model of partial sciatic nerve ligation after daily subcutaneous administration of 0.1 mg/kg a week before and two weeks after surgery. Mechanical allodynia and thermal hyperalgesia were evaluated in 46 rats allocated to receive: (1) Vehicle (before surgery) – Vehicle (after surgery); (2) Vehicle – WIN55,212-2; (3) WIN55,212-2 – Vehicle; (4) WIN55,212-2 – WIN55,212-2; (5) AM251 + vehicle; (6) AM251 + WIN55,212-2; (7) AM630 + vehicle; (8) AM630 + WIN55,212-2; (9) Sham receiving vehicle; and (10) Sham receiving WIN55,212-2. The decreased in mechanical allodynia and thermal hyperalgesia by WIN55,212-2 was significantly greater when it was administered during one week before surgery. **In conclusion, pre-emptive use of cannabinoids produced greater antinociceptive effects in a model of neuropathic pain and this effect is mediated by cannabinoid CB1 and CB2 receptors.**

Trigeminal Neuropathic Pain

Neuropharmacology
Volume 53, Issue 1, July 2007, Pages 169-177

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The synthetic cannabinoids attenuate allodynia and hyperalgesia in a rat model of trigeminal neuropathic pain

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Received 20 December 2006; revised 26 April 2007; accepted 27 April 2007. Available online 13 May 2007.

Abstract

Trigeminal neuralgia is a disorder of paroxysmal and severely disabling facial pain and continues to be a real therapeutic challenge. At present there are few effective drugs. Here we have evaluated the effects of the synthetic cannabinoid WIN 55,212-2 on mechanical allodynia and thermal hyperalgesia in a rat model of trigeminal neuropathic pain produced by a chronic constriction injury (CCI) of the infraorbital branch of the trigeminal nerve (ION). Relative to sham operation controls, rats with the CCI-ION consistently displayed hyperresponsiveness to von Frey filament and heat stimulation of the vibrissal pad. Both mechanical allodynia and thermal hyperalgesia are seen both ipsilateral and contralateral to the side of nerve injury, but is significantly more severe ipsilaterally. Administration of WIN 55,212-2 (0.3–5 mg/kg i.p.) dose-dependently increased the mechanical and heat withdrawal thresholds. WIN 55,212-2 (0.3–3 mg/kg i.p.) produced no significant motor deficits in animals using the rotarod test. The effect of WIN 55,212-2 was mimicked by cannabinoid CB1 receptor agonist HU 210 and was antagonized by CB1 receptor antagonist AM 251, but not by CB2 receptor antagonist AM 630 or vanilloid receptor 1 antagonist capsazepine, suggesting the involvement of CB1 receptors. CCI-ION also induced a time-dependent upregulation of CB1 receptors primarily within the ipsilateral superficial laminae of the trigeminal caudal nucleus revealed by both Western blot and immunohistochemistry. **Taken together, these results suggest that cannabinoids may be a useful therapeutic approach for the clinical management of trigeminal neuropathic pain disorders.**

Reproductive System

Critical Developmental Periods

The endocannabinoid system: function in survival of the embryo, the newborn and the neuron.

Review
Neuroreport. 13(15):1833-1841, October 28, 2002.
Fride, Ester; Shohami, Esther 1 2 CA
Abstract:
Since the identification and cloning of the first cannabinoid (CB1) receptor and the subsequent discovery of the endogenous cannabinoid ligands (endocannabinoids), anandamide, 2-arachidonoyl glycerol (2-AG) and noladin ether, a intensive search for their function in health and disease has been launched. The endocannabinoids in the central nervous system bind Gi/o coupled CB1 receptors that modulate adenylyl cyclase, ion channels and extracellular signal-regulated kinases. The present review discusses the nature of endocannabinoid (anandamide and 2-AG) neurotransmission, the in vivo activity of cannabinoids and the possibility that some of these activities are mediated via a receptor, yet to be discovered, which is distinct from the brain specific

CB1 receptor. Three physiological functions in which the endocannabinoids play a critical role are also discussed: embryonal implantation, feeding and appetite, and neuroprotection.
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Colostrum (Breast Milk)

Journal of Pediatric Research
November 2007, 62:5 > Inhi

Inhibition of Milk Ingestion and Growth After Administration of a Neutral Cannabinoid CB1 Receptor Antagonist on the First Postnatal Day in the Mouse.

Articles
Pediatric Research. 62(5):533-536, November 2007.
FRIDE, ESTER; BRAUN, HILIT; MATAN, HILA; STEINBERG, SHACHAR; REGGIO, PATRICIA H.; SELTZMAN, HERBERT H.
Abstract:
We have shown previously that neonatal exposure to the cannabinoid CB1 receptor antagonist/inverse agonist rimonabant (SR141716) interfered with suckling and development. However, it was not clear whether the developmental deficiencies were induced by neutral CB1 receptor blockade, thereby inhibiting endogenous cannabinoid "tone," or by inverse agonist reduction of constitutive CB1 receptors. CB1 receptor blockade supports our hypothesis that low CB1 receptor concentrations and/or reduced endocannabinoid levels underlie infant nonorganic failure to thrive (NOFTT). Inverse agonism implies that lower constitutive CB1 receptor activity may be responsible for impaired food intake in newborns. In the present study, we injected the neutral CB1 receptor antagonist 5-(4-chlorophenyl)-3-[(E)-2-cyclohexylethenyl]-1-(2,4-dichlorophenyl)-4-methyl-1H-pyrazole (VCHSR1) to 1-d-old mouse pups and recorded weight gain, gastric milk contents (milkbands), axillary temperature, and survival between age 1 and 10 d. The results showed a dose-related interference with all measures. These data show that (1) growth failure induced by rimonabant is generalized to another CB1 antagonist and (2) cannabinoid CB1 receptor activation by endocannabinoids is essential for normal milk ingestion and development in mice. **This supports our hypothesis that endocannabinoid deficiency and perhaps CB1 receptor dysfunction represents the uncharacterized biologic vulnerability, which underlies NOFTT.**
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Sperm

General and Comparative Endocrinology
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Short Communication

Endocannabinoid control of sperm motility: The role of epididymus

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Received 16 September 2006; revised 30 January 2007; accepted 2 February 2007.
Available online 12 February 2007.

Abstract
Endocannabinoids are endogenous ligands for plasma membrane receptors (CB1 and CB2), belonging to the superfamily of G-protein-coupled receptors. They mimic some of the effects played by D9-tetrahydrocannabinol (THC), the active principle isolated from Cannabis sativa. N-arachidonoylethanolamine (anandamide, AEA) is the main endocannabinoid described to date in the testis and in human seminal plasma. However, the activity of AEA in controlling male reproduction is still poorly understood. In this study we report on physiological activity of endocannabinoids in the male reproductive tract. Using wild type (WT) and CB1 knock out mice (CB1KO) we show that endocannabinoids act in the epididymus. **Here, through CB1, they inhibit sperm motility measured as the percentage of motile spermatozoa (SPZ). In particular, while in WT mice, as expected, the percentage of motile SPZ (measured in caput and cauda of epididymus) was significantly lower in the caput as compared with the cauda, in CB1KO mice a strong increase of motile SPZ in the caput was measured.**

Uterine Receptivity

Originally published In Press as doi:10.1074/jbc.M100679200 on March 8, 2001
J. Biol. Chem., Vol. 276, Issue 23, 20523-20528, June 8, 2001

*Dysregulated Cannabinoid Signaling Disrupts Uterine Receptivity for Embryo Implantation**

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The mechanisms by which synchronized embryonic development to the blastocyst stage, preparation of the uterus for the receptive state, and reciprocal embryo-uterine interactions for implantation are coordinated are still unclear. We show in this study that preimplantation embryo development became asynchronous in mice that are deficient in brain-type (CB1) and/or spleen-type (CB2) cannabinoid receptor genes. Furthermore, whereas the levels of uterine anandamide (endocannabinoid) and blastocyst CB1 are coordinately down-regulated with the onset of uterine receptivity and blastocyst activation prior to implantation, these levels remained high in the nonreceptive uterus and in dormant blastocysts during delayed implantation and in pregnant, leukemia inhibitory factor (LIF)-deficient mice with implantation failure. These results suggest that a tight regulation of endocannabinoid signaling is important for synchronizing embryo development with uterine receptivity for implantation. **Indeed this is consistent with our finding that while an experimentally induced, sustained level of an exogenously administered, natural cannabinoid inhibited implantation in wild-type mice, it failed to do so in CB1//CB2/ double mutant mice. The present study is clinically important because of the widely debated medicinal use of cannabinoids and their reported adverse effects on pregnancy.**

* This work was supported by National Institutes of Health Grants DA 06668, HD 12304, and HD 29968 (to S. K. D.), HD 37394 (to B. C. P.), and GM 45741 (to H. H. O. S.) and by the Hormel Foundation (to H. H. O. S.). Center grants in Reproductive Biology (HD 33994) and Mental Retardation (HD 02528) provided access to various core facilities.The costs of publication of this article were defrayed in part by

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Uterus

Prostaglandins &Other Lipid Mediators
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Differential regulation of endocannabinoid synthesis and degradation in the uterus during embryo implantation

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Received 28 August 2006; revised 27 September 2006; accepted 28 September 2006.
Available online 28 November 2006.

Abstract
Preimplantation embryo development to the blastocyst stage and uterine differentiation to the receptive state are prerequisites for embryo implantation. Burgeoning evidence suggests that endocannabinoid signaling is critical to early pregnancy events.

Anandamide (N-arachidonoylethanolamine) and 2-AG (2-arachidonoylglycerol) are two major endocannabinoids that bind to and activate G-protein coupled cannabinoid receptors CB1 and CB2. We have previously shown that a physiological tone of anandamide is critical to preimplantation events in mice, since either silencing or amplification of anandamide signaling causes retarded development and oviductal retention of embryos via CB1, leading to deferred implantation and compromised pregnancy outcome. Whether 2-AG, which also influences many biological functions, has any effects on early pregnancy remains unknown. Furthermore, mechanisms by which differential uterine endocannabinoid gradients are established under changing pregnancy state is not clearly understood. We show here that 2-AG is present at levels one order of magnitude higher than those of anandamide in the mouse uterus, but with similar patterns as anandamide, i.e. lower levels at implantation sites and higher at interimplantation sites. We also provide evidence that region- and stage-specific uterine expression of N-acylphosphatidylethanolamine-specific phospholipase D (NAPE-PLD) and fatty acid amide hydrolase (FAAH), and sn-1-diacylglycerol (DAG) lipase α (DAGLα) and monoacylglycerol lipase (MAGL) for synthesis and hydrolysis of anandamide and 2-AG, respectively, creates endocannabinoid gradients conducive to implantation. Our genetic evidence suggests that FAAH is the major degrading enzyme for anandamide, whereas COX-2, MAGL and to some extent COX-1 participate in metabolizing 2-AG in the pregnant uterus. **The results suggest that aberrant functioning of these pathways impacting uterine anandamide and/or 2-AG levels would compromise pregnancy outcome.**

Liver Disease

Cerebral Disfunction Following Liver Failure

(The FASEB Journal. 2007;21:2431-2441.)
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Cannabinoids ameliorate cerebral dysfunction following liver failure via AMP-activated protein kinase

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Hepatic encephalopathy (HE) is a neuropsychiatric disorder of complex pathogenesis caused by acute or chronic liver failure. We studied the etiology of cerebral dysfunction in a murine model of HE induced by either bile duct ligation or thioacetamideadministration. We report that stimulation of cerebral AMP-activated protein kinase (AMPK), a major intracellular energy sensor,is a compensatory response to liver failure. This function of AMPK is regulated by endocannabinoids. The cannabinoid systemcontrols systemic energy balance via the cannabinoid receptors CB-1 and CB-2. Under normal circumstances, AMPK activity ismediated by CB-1 while CB-2 is barely detected. However, CB-2 is strongly stimulated in response to liver failure. Administration of 9-tetrahydrocannabinol (THC) augmented AMPK activity and restored brain function in WT mice but not in their CB-2 KO littermates. **These results suggest that HE is a disease of energy flux. CB-2 signaling is a cerebral stress response mechanism and makes AMPK a promising target for its treatment by modulating the cannabinoid system.**—Dagon, Y., Avraham, Y., Ilan, Y., Mechoulam, R., Berry, E. M. Cannabinoids ameliorate cerebral dysfunction following liver failure via AMP-activated protein kinase.

Respiratory System Disorders

Asthma

Toxicology and Applied Pharmacology
Volume 188, Issue 1, 1 April 2003, Pages 24-35

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Regular article

Attenuation of the ovalbumin-induced allergic airway response by cannabinoid treatment in A/J mice *1

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Received 12 July 2002; accepted 19 December 2002. ; Available online 11 March 2003.

Abstract
T cells are sensitive to modulation by cannabinoids as evidenced by their ability to inhibit expression of cytokines, including interleukin (IL)-2 and IL-4. Because T cells play a key role in the pathophysiology of allergic asthma by expressing T helper cell (Th)2 cytokines, the objective of the present studies was to examine the effect of cannabinoids on immunologic and pathologic features associated with the allergic airway response induced by ovalbumin (Ova). A/J mice were systemically sensitized with Ova and subsequently challenged with aerosolized Ova. The steady-state mRNA expression of IL-2 and Th2 cytokines (IL-4, IL-5, and IL-13) was markedly increased in the lungs of Ova-sensitized mice 24 h after a single Ova challenge. Concordantly, the level of total and Ova-specific serum immunoglobulin (Ig)E and intraepithelial mucosubstances in the axial intrapulmonary airway of Ova-sensitized mice was robustly elevated 96 h after the second Ova challenge. Cannabinol (CBN) or Δ9-tetrahydrocannabinol (Δ9-THC; 50 mg/kg, ip), administered daily for 3 consecutive days before sensitization and then before challenge, significantly attenuated the elevation of IL-2, IL-4, IL-5, and IL-13 steady-state mRNA expression elicited by Ova challenge in the lungs. In addition, the elevation of serum IgE and the mucus overproduction induced by Ova challenge was also markedly attenuated by CBN or Δ9-THC administration in Ova-sensitized mice. **These results suggest that plant-derived immunomodulatory cannabinoids exhibit potential therapeutic utility in the treatment of allergic airway disease by inhibiting the expression of critical T cell cytokines and the associated inflammatory response.**

Broncoconstriction

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Cannabinoid CB2 receptor activation prevents bronchoconstriction and airway oedema in a model of gastro-oesophageal reflux

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Abstract
Cannabinoids have been shown to inhibit sensory nerve activation in guinea-pigs and humans. Their effects are mediated by specific activation of two types of receptors, named CB1 and CB2. The purpose of this study was to investigate the effects of WIN 55,212-2, (R)-(+)-[2,3-dihydro-5methyl-3-[(4-morpholino)methyl]pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl](1-naphthyl)methanone, a non selective agonist of cannabinoid receptors, and JWH 133, (6aR,10aR)-3-(1,1-dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran a selective cannabinoid CB2receptor agonist, on the sensory nerve component of intraoesophageal (i.oe.) HCl-induced airway microvascular leakage and bronchoconstriction in guinea-pigs. We also tested the effect of WIN 55,212-2 on substance P-induced plasma extravasation and bronchoconstriction. Airway microvascular leakage and bronchoconstriction induced by i.oe. HCl was inhibited by the cannabinoid CB1/CB2 agonist WIN 55,212-2 (0.3–3 mg/kg i.p.) in a dose-dependent manner (maximal inhibition at the dose of 3 mg kg– 1, $P < 0.01$). The effect of WIN 55,212-2 was inhibited by a cannabinoid CB2 receptor antagonist SR 144528, [N-[(1S)-endo-1,3,3-trimethylbicyclo[2,2,1] heptan-2yl]-5-(-4-chloro-3-methylphenyl)-1-(4-methylbenzyl)pyrazole-3-carboxamide], but not by a CB1 receptor antagonist, SR 141716, [N-(piperidin-1yl)-5-(-4-chlorophenyl)-1-(2,4dichlorophenyl)-4-methyl-1H-pyrazole-3-carboxamide hydrochloride]. The cannabinoid CB2agonist JWH 133 (0.3–3 mg/kg i.p.) mimicked the inhibitory effect of WIN 55,212-2 on HCl-induced microvascular leakage. Under similar conditions, WIN 55,212-2 (1 mg kg – 1 i.p.) was unable to counteract the airway microvascular leakage and bronchoconstriction induced by substance P. **These results suggest that inhibition by WIN 55,212-2 of airway plasma extravasation and bronchoconstriction induced by i.oe. HCl instillation in guinea-pigs is mediated through cannabinoid CB2 receptor activation.**

Influenza

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INFLAMMATION, IMMUNOPHARMACOLOGY, AND ASTHMA

Modulation of Airway Responses to Influenza A/PR/8/34 by 9-Tetrahydrocannabinol in C57BL/6 Mice

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9-Tetrahydrocannabinol (9-THC) has been widely established as a modulator of host immune responses. Accordingly, the objective of the present study was to examine the effects of 9-THC on the immune response within the lungs and associated changes in the morphology of the bronchiolar epithelium after one challenge with a nonlethal dose of the influenza virus A/PR/8 (PR8). C57BL/6 mice were treated by oral gavage with 9-THC and/or vehicle (corn oil) for 5 consecutive days. On day 3, mice were instilled intranasally with 50 plaque-forming units of PR8 and/or vehicle (saline) 4 h before 9-THC exposure. Mice were subsequently killed 7 and 10 days postinfection (dpi). Viral hemagglutinin 1 (H1) mRNA levels in the lungs were increased in a dose-dependent manner with 9-THC treatment. Enumeration of inflammatory cell types in bronchoalveolar lavage fluid showed an attenuation of macrophages and CD4+ and CD8+ T cells in 9-THC-treated mice compared with controls. **Likewise, the magnitude of inflammation and virus-induced mucous cell metaplasia, as assessed by histopathology, was reduced in 9-THC-treated mice by 10 dpi**. Collectively, these results suggest that 9-THC treatment increased viral load, as assessed by H1 mRNA levels, through a decrease in recruitment of macrophages and lymphocytes, particularly CD4+ and CD8+ T cells, to the lung.

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Vaporization

Decreased respiratory symptoms in cannabis users who vaporize

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Abstract
Cannabis smoking can create respiratory problems. Vaporizers heat cannabis to release active cannabinoids, but remain cool enough to avoid the smoke and toxins associated with combustion. Vaporized cannabis should create fewer respiratory symptoms than smoked cannabis. We examined self-reported respiratory symptoms in participants who ranged in cigarette and cannabis use. Data from a large Internet sample revealed that the use of a vaporizer predicted fewer respiratory symptoms even when age, sex, cigarette smoking, and amount of cannabis used were taken into account. Age, sex, cigarettes, and amount of cannabis also had significant effects. The number of cigarettes smoked and amount of cannabis used interacted to create worse respiratory problems. A significant interaction revealed that the impact of a vaporizer

was larger as the amount of cannabis used increased. These data suggest that the safety of cannabis can increase with the use of a vaporizer. Regular users of joints, blunts, pipes, and water pipes might decrease respiratory symptoms by switching to a vaporizer

Background

Cannabis smoke contains gaseous and particulate matter with the potential to create symptoms of respiratory problems [1]. Although cannabis creates fewer problems than cigarette smoking [2], increasing its safety has the potential to improve quality of life. One step toward increasing the safety of cannabis involves the use of vaporizers. Vaporizers heat cannabis to temperatures that release cannabinoids in a fine mist without creating the toxins associated with combustion [3,4]. Although vaporizers are not common knowledge in popular culture, a recent photograph of one appeared in the New England Journal of Medicine [5], and information about the machine is becoming more available. A vaporizer has the potential to increase the safety of cannabis use, but data from human users appear only rarely [4].

The potential for cannabis-induced lung problems is particularly important in light of frequent concurrent tobacco smoking. Cannabis use may prove especially detrimental in the production of respiratory symptoms in cigarette smokers. For example, one study revealed increased respiratory symptoms in cannabis dependent 21-year-olds, but particularly in those who also smoked cigarettes. Cannabis dependence in the absence of cigarette use led to symptoms comparable to smoking 1–10 cigarettes per day, but quickly escalated when cannabis and tobacco were combined [6].

Method

We sought to identify the impact of vaporizers on respiratory symptoms. In an effort to target frequent cannabis users, three organizations committed to reforming drug laws were asked to send a query to their mailing lists for participation in a survey. Participants responded to an email request and had a chance to win a cash prize. Approximately 9,000 people replied, but we focused on those who had used cannabis at least once in the previous month. (More details of the data collection appear in a paper addressing other aspects of this sample [7].) In an effort to minimize the impact of other sources of respiratory symptoms, only those respondents who did not have cystic fibrosis or asthma and had never inhaled other drugs (inhalants, heroin, methamphetamine, or crack cocaine) were included. Those who reported that their primary method of administration of cannabis was oral ingestion were also omitted, because eating the plant should have no smoke-inhalation-induced respiratory effects.

Participants

The 6,883 people who qualified included 4,493 men (65.3%) and 2,390 women. Ages ranged from 18 to 88 (Mean = 31.3, SD = 12.4). Education ranged from some high school to advanced degrees, with a median of some college but not a degree. Median income was $20,000 to $40,000 per year. Respondents were primarily Caucasian (87%) but included African Americans (1%), Native Americans (3%), Asians (3%) Latinos (4%), and people of mixed race (2%). Participants reported that their first cannabis use was at a mean age of 16.7 (SD = 4.2).

Measures

Respiratory symptoms

Participants reported respiratory symptoms by answering six questions: Do you usually have a cough? Does your chest sound wheezy or whistling other than from colds? Are you troubled by shortness of breath when hurrying on the level ground or walking up a slight hill? Do you have to walk slower than most people your own age on the level ground because of breathlessness? Do you cough up phlegm in the morning? and Do you wake up at night with tightness in your chest? These questions revealed respiratory problems in cannabis-dependent individuals in previous work [6]. Symptoms were not particularly common (mean of the total symptom count = 0.80, SD = 1.1), but ranged from 0 to 6.

The sum of these items had significant skew that would preclude the use of parametric statistics, so we created two groups of participants: those who did (N = 3,016) and did not (N = 3,867) report respiratory problems. This dichotomized outcome served as the dependent variable.

Vaporizer use

Participants reported the technique they used most frequently when ingesting marijuana, and chose from blunts, joints, water pipes, pipes, edibles, vaporizers, and other. Only 152 participants (2.2%) reported vaporizing as their primary method for cannabis use.

Marijuana use

Although assessing the frequency of marijuana use has proven comparable to assessing the frequency of use for other drugs, assessing the quantity of consumption remains quite difficult. Standard units comparable to those found with alcohol or cigarettes are unavailable. Because respiratory effects of marijuana should covary with the amount used rather than the simple frequency of use, we asked participants to estimate the amount of marijuana they consumed per week in 1-gram joint equivalents. This rough estimate is necessarily imperfect, but has proven useful in previous work [8]. Participants reported amount of cannabis use in one-gram joint equivalents, which averaged 9.4 grams per week (SD = 11.9).

Cigarettes

Those who smoked cigarettes (4,829) began at a mean age of 16.0 (SD = 3.4). Cigarette smoking was generally light. Mean cigarettes per day was 8.6 (SD = 10.7) but ranged as high as 4 packs per day.

Results

A simple chi-square test revealed that vaporizer users were less likely to report respiratory problems than participants who did not vaporize, with 100 of 152 vaporizer users (65.8%) reporting no respiratory problems, compared to 3767 of 6731 (56.0%), chi-square (1) = 5.8, p < .05. This analysis provided a rough look at the potential for vaporizers, and suggested that the machines could improve respiratory symptoms. Nevertheless, this analytic approach did not account for important covariates or address potential interactions, so we used logistic regression. We computed interactions by centering the variables to correct for non-essential multicollinearity and then multiplying [9]. We report the full model with all two-way interactions and the three-way interaction present, but deleting any of these effects did

not change the pattern of results. A logistic regression analysis with age and sex as covariates revealed main effects for cigarettes, cannabis use, and vaporizer use. The interaction of cigarettes and marijuana was significant, as revealed in previous work [6]. In addition the interaction of marijuana use and vaporizer use was significant, all p-values < .05. (See Table 1.)
Table 1. Predicting Respiratory Symptoms (N = 6,883)

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Vision

Glaucoma

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PERSPECTIVE

Cannabinoids and glaucoma

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Glaucoma is one of the leading causes of blindness in the world. In spite of the diverse therapeutic possibilities, new and better treatments for glaucoma are highly desirable. Cannabinoids effectively lower the intraocular pressure (IOP) and have neuroprotective actions. Thus, they could potentially be useful in the

treatment of glaucoma. The purpose of this article is to provide the reader with an overview of the latest achievements in research into the potential use of cannabinoids for glaucoma.

Journal of Glaucoma

October 2006, 15:5 > Effect of Sublingual Application...

Effect of Sublingual Application of Cannabinoids on Intraocular Pressure: A Pilot Study.

Original Studies

Journal of Glaucoma. 15(5):349-353, October 2006.
Tomida, Ileana MD *; Azuara-Blanco, Augusto MD, PhD *; House, Heather BSc +; Flint, Maggie BSc ++; Pertwee, Roger G. DPhil, DSc [S]; Robson, Philip J. MD +
Abstract:
Purpose: The purpose of this study was to assess the effect on intraocular pressure (IOP) and the safety and tolerability of oromucosal administration of a low dose of delta-9-tetrahydrocannabinol ([DELTA]-9-THC) and cannabidiol (CBD).
Patients and Methods: A randomized, double-masked, placebo-controlled, 4 way crossover study was conducted at a single center, using cannabis-based medicinal extract of [DELTA]-9-THC and CBD. Six patients with ocular hypertension or early primary open angle glaucoma received a single sublingual dose at 8 AM of 5 mg [DELTA]-9-THC, 20 mg CBD, 40 mg CBD, or placebo. Main outcome measure was IOP. Secondary outcomes included visual acuity, vital signs, and psychotropic effects.
Results: Two hours after sublingual administration of 5 mg [DELTA]-9-THC, the IOP was significantly lower than after placebo (23.5 mm Hg vs. 27.3 mm Hg, P=0.026). The IOP returned to baseline level after the 4-hour IOP measurement. CBD administration did not reduce the IOP at any time. However, the higher dose of CBD (40 mg) produced a transient elevation of IOP at 4 hours after administration, from 23.2 to 25.9 mm Hg (P=0.028). Vital signs and visual acuity were not significantly changed. One patient experienced a transient and mild paniclike reaction after [DELTA]-9-THC administration.
Conclusions: A single 5 mg sublingual dose of [DELTA]-9-THC reduced the IOP [inter ocular pressure] temporarily and was well tolerated by most patients. Sublingual administration of 20 mg CBD did not reduce IOP, whereas 40 mg CBD produced a transient increase IOP rise.