Cannabis and Cancer

Studies Showing an Anti-Cancer Effect

A Population-Based Case-Control Study of Marijuana Use and Head and Neck Squamous Cell Carcinoma

Caihua Liang,1 Michael D. McClean,3 Carmen Marsit,2 Brock Christensen,1,2 Edward Peters,4 Heather H. Nelson5 and Karl T. Kelsey1,2

Cannabinoids, constituents of marijuana smoke, have been recognized to have potential antitumor properties. However, the epidemiologic evidence addressing the relationship between marijuana use and the induction of head and neck squamous cell carcinoma (HNSCC) is inconsistent and conflicting.

[PDF]

Glioma

Parolaro and Massi. 2008. Cannabinoids as a potential new drug therapy for the treatment of gliomas. Expert Reviews of Neurotherapeutics 8: 37-49
[PDF]

Galanti et al. 2007. Delta9-Tetrahydrocannabinol inhibits cell cycle progression by downregulation of E2F1 in human glioblastoma multiforme cells. Acta Oncologica 12: 1-9.
Abstract

Calatozzolo et al. 2007. Expression of cannabinoid receptors and neurotrophins in human gliomas. Neurological Sciences 28: 304-310.
Abstract

Lung Cancer

Preet et al. 2008. Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. Oncogene 10: 339-346.
http://www.nature.com/onc/journal/v27/n3/abs/1210641a.html

Pancreatic Cancer --

Michalski et al. 2007. Cannabinoids in pancreatic cancer: correlation with survival and pain. International Journal of Cancer (E-pub ahead of print).

Cervical Cancer --

Ramer and Hinz. 2008. Inhibition of cancer cell invasion by cannabinoids via increased cell expression of tissue inhibitor of matrix metalloproteinases-1. Journal of the National Cancer Institute 100: 59-69.
http://jnci.oxfordjournals.org/cgi/content/abstract/djm268v1

Breast Cancer --

McAllister et al. 2007. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. Molecular Cancer Therapeutics 6: 2921-2927.
http://mct.aacrjournals.org/cgi/content/abstract/6/11/2921

Turned-off Cannabinoid Receptor Turns on Colorectal Tumor Growth

New preclinical research shows that cannabinoid cell surface receptor CB1 plays a tumor-suppressing role in human colorectal cancer, scientists report in the Aug. 1 edition of the journal Cancer Research.

CB1 is well-established for relieving pain and nausea, elevating mood and stimulating appetite by serving as a docking station for the cannabinoid group of signaling molecules. It now may serve as a new path for cancer prevention or treatment. "We've found that CB1 expression is lost in most colorectal cancers, and when that happens a cancerpromoting protein is free to inhibit cell death," said senior author Raymond DuBois, M.D., Ph.D., provost and executive vice president of The University of Texas M. D. Anderson Cancer Center.

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

McAllister, S.D. , Christian, R.T., Horowitz, M.P., Garcia, A. and Desprez. P (2007
Molecular Cancer Therapeutics Nov. 6 (11).

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]
Molecular Cancer Therapeutics 6, 2921-2927, November 1, 2007. doi: 10.1158/1535-7163.MCT-07-0371

British Journal of Cancer (2006) 95, 197-203. doi:10.1038/sj.bjc.6603236
Published online 27 June 2006

A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme

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Delta9-Tetrahydrocannabinol (THC) and other cannabinoids inhibit tumour growth and angiogenesis in animal models, so their potential application as antitumoral drugs has been suggested. However, the antitumoral effect of cannabinoids has never been tested in humans. Here we report the first clinical study aimed at assessing cannabinoid antitumoral action, specifically a pilot phase I trial in which nine patients with recurrent glioblastoma multiforme were administered THC intratumoraly. The patients had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumour progression. The primary end point of the study was to determine the safety of intracranial THC administration. We also evaluated THC action on the length of survival and various tumour-cell parameters. A dose escalation regimen for THC administration was assessed. Cannabinoid delivery was safe and could be achieved without overt psychoactive effects. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% confidence interval: 15-33). Delta9-Tetrahydrocannabinol inhibited tumour-cell proliferation in vitro and decreased tumour-cell Ki67 immunostaining when administered to two patients. The fair safety profile of THC, together with its possible antiproliferative action on tumour cells reported here and in other studies, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids.

http://www.nature.com/bjc/journal/v95/n2/abs/6603236a.html

Inhibition of Glioma Growth in Vivo by Selective Activation of the CB2 Cannabinoid Receptor1

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The development of new therapeutic strategies is essential for the management of gliomas, one of the most malignant forms of cancer. We have shown previously that the growth of the rat glioma C6 cell line is inhibited by psychoactive cannabinoids (I. Galve-Roperh et al., Nat. Med., 6: 313-319, 2000). These compounds act on the brain and some other organs through the widely expressed CB1 receptor. By contrast, the other cannabinoid receptor subtype, the CB2 receptor, shows a much more restricted distribution and is absent from normal brain. Here we show that local administration of the selective CB2 agonist JWH-133 at 50 µg/day to Rag-2-/- mice induced a considerable regression of malignant tumors generated by inoculation of C6 glioma cells. The selective involvement of the CB2 receptor in this action was evidenced by: (a) the prevention by the CB2 antagonist SR144528 but not the CB1 antagonist SR141716; (b) the down-regulation of the CB2 receptor but not the CB1 receptor in the tumors; and (c) the absence of typical CB1-mediated psychotropic side effects. Cannabinoid receptor expression was subsequently examined in biopsies from human astrocytomas. A full 70% (26 of 37) of the human astrocytomas analyzed expressed significant levels of cannabinoid receptors. Of interest, the extent of CB2 receptor expression was directly related with tumor malignancy. In addition, the growth of grade IV human astrocytoma cells in Rag-2-/- mice was completely blocked by JWH-133 administration at 50 µg/day. Experiments carried out with C6 glioma cells in culture evidenced the internalization of the CB2 but not the CB1 receptor upon JWH-133 challenge and showed that selective activation of the CB2 receptor signaled apoptosis via enhanced ceramide synthesis de novo. These results support a therapeutic approach for the treatment of malignant gliomas devoid of psychotropic side effects.

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Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation.

Galve-Roperh I, Sanchez C, Cortes ML, del Pulgar TG, Izquierdo M, Guzman M.

Department of Biochemistry and Molecular Biology I, School of Biology, Complutense University, 28040-Madrid, Spain.

Delta9-Tetrahydrocannabinol, the main active component of marijuana, induces apoptosis of transformed neural cells in culture. Here, we show that intratumoral administration of Delta9-tetrahydrocannabinol and the synthetic cannabinoid agonist WIN-55,212-2 induced a considerable regression of malignant gliomas in Wistar rats and in mice deficient in recombination activating gene 2. Cannabinoid treatment did not produce any substantial neurotoxic effect in the conditions used. Experiments with two subclones of C6 glioma cells in culture showed that cannabinoids signal apoptosis by a pathway involving cannabinoid receptors, sustained ceramide accumulation and Raf1/extracellular signal-regulated kinase activation. These results may provide the basis for a new therapeutic approach for the treatment of malignant gliomas.
PMID: 10700234 [PubMed - indexed for MEDLINE]

1: Biochem Pharmacol 2001 Sep 15;62(6):755-63

Antitumor effects of ajulemic acid (CT3), a synthetic non-psychoactive cannabinoid.

Recht LD, Salmonsen R, Rosetti R, Jang T, Pipia G, Kubiatowski T, Karim P, Ross AH, Zurier R, Litofsky NS, Burstein S.

Department of Neurology, University of Massachusetts Medical School, 55 Lake Avenue North, Worcester, MA 01655, USA. RECHTL@ummh.org

One of the endogenous transformation products of tetrahydrocannabinol (THC) is THC-11-oic acid, and ajulemic acid (AJA; dimethylheptyl-THC-11-oic acid) is a side-chain synthetic analog of THC-11-oic acid. In preclinical studies, AJA has been found to be a potent anti-inflammatory agent without psychoactive properties. Based on recent reports suggesting antitumor effects of cannabinoids (CBs), we assessed the potential of AJA as an antitumor agent. AJA proved to be approximately one-half as potent as THC in inhibiting tumor growth in vitro against a variety of neoplastic cell lines. However, its in vitro effects lasted longer. The antitumor effect was stereospecific, suggesting receptor mediation. Unlike THC, however, whose effect was blocked by both CB(1) and CB(2) receptor antagonists, the effect of AJA was inhibited by only the CB(2) antagonist. Additionally, incubation of C6 glioma cells with AJA resulted in the formation of lipid droplets, the number of which increased over time; this effect was noted to a much greater extent after AJA than after THC and was not seen in WI-38 cells, a human normal fibroblast cell line. Analysis of incorporation of radiolabeled fatty acids revealed a marked accumulation of triglycerides in AJA-treated cells at concentrations that produced tumor growth inhibition. Finally, AJA, administered p.o. to nude mice at a dosage several

orders of magnitude below that which produces toxicity, inhibited the growth of subcutaneously implanted U87 human glioma cells modestly but significantly. We conclude that AJA acts to produce significant antitumor activity and effects its actions primarily via CB(2) receptors. Its very favorable toxicity profile, including lack of psychoactivity, makes it suitable for chronic usage. Further studies are warranted to determine its optimal role as an antitumor agent.
PMID: 11551521 [PubMed - indexed for MEDLINE]

Biochem J 2001 Aug 15;358(Pt 1):249-55 Related Articles, Books, LinkOut

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Palmitoylethanolamide inhibits the expression of fatty acid amide hydrolase and enhances the anti-proliferative effect of anandamide in human breast cancer cells.

Di Marzo V, Melck D, Orlando P, Bisogno T, Zagoory O, Bifulco M, Vogel Z, De Petrocellis L.
Istituto per la Chimica di Molecole di Interesse Biologico, Via Toiano 6, 80072, Arco Felice, Napoli, Italy. vdimarzo@icmib.na.cnr.it

Palmitoylethanolamide (PEA) has been shown to act in synergy with anandamide (arachidonoylethanolamide; AEA), an endogenous agonist of cannabinoid receptor type 1 (CB(1)). This synergistic effect was reduced by the CB(2) cannabinoid receptor antagonist SR144528, although PEA does not activate either CB(1) or CB(2) receptors. Here we show that PEA potently enhances the anti-proliferative effects of AEA on human breast cancer cells (HBCCs), in part by inhibiting the expression of fatty acid amide hydrolase (FAAH), the major enzyme catalysing AEA degradation. PEA (1-10 microM) enhanced in a dose-related manner the inhibitory effect of AEA on both basal and nerve growth factor (NGF)-induced HBCC proliferation, without inducing any cytostatic effect by itself. PEA (5 microM) decreased the IC(50) values for AEA inhibitory effects by 3-6-fold. This effect was not blocked by the CB(2) receptor antagonist SR144528, and was not mimicked by a selective agonist of CB(2) receptors. PEA enhanced AEA-evoked inhibition of the expression of NGF Trk receptors, which underlies the anti-proliferative effect of the endocannabinoid on NGF-stimulated MCF-7 cells. The effect of PEA was due in part to inhibition of AEA degradation, since treatment of MCF-7 cells with 5 microM PEA caused a approximately 30-40% down-regulation of FAAH expression and activity. However, PEA also enhanced the cytostatic effect of the cannabinoid receptor agonist HU-210, although less potently than with AEA. PEA did not modify the affinity of ligands for CB(1) or CB(2) receptors, and neither did it alter the CB(1)/CB(2)-mediated inhibitory effect of AEA on adenylate cyclase type V, nor the expression of CB(1) and CB(2) receptors in MCF-7 cells. We suggest that long-term PEA treatment of cells may positively affect the pharmacological activity of AEA, in part by inhibiting FAAH expression.
PMID: 11485574 [PubMed - indexed for MEDLINE]

Prostaglandins Other Lipid Mediat 2000 Apr;61(1-2):43-61Related Articles,

Books, LinkOut

Cannabimimetic fatty acid derivatives in cancer and inflammation.

Di Marzo V, Melck D, De Petrocellis L, Bisogno T.
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Evidence for the role of the cannabimimetic fatty acid derivatives (CFADs), i.e. anandamide (arachidonoylethanolamide, AEA), 2-arachidonoylglycerol (2-AG) and palmitoylethanolamide (PEA), in the control of inflammation and of the proliferation of tumor cells is reviewed here. The biosynthesis of AEA, PEA, or 2-AG can be induced by stimulation with either Ca(2+) ionophores, lipopolysaccharide, or platelet activating factor in macrophages, and by ionomycin or antigen challenge in rat basophilic leukemia (RBL-2H3) cells (a widely used model for mast cells). These cells also inactivate CFADs through re-uptake and/or hydrolysis and/or esterification processes. AEA and PEA modulate cytokine and/or arachidonate release from macrophages in vitro, regulate serotonin secretion from RBL-2H3 cells, and are analgesic in some animal models of inflammatory pain. However, the involvement of endogenous CFADs and cannabinoid CB(1) and CB(2) receptors in these effects is still controversial. In human breast and prostate cancer cells, AEA and 2-AG, but not PEA, potently inhibit prolactin and/or nerve growth factor (NGF)-induced cell proliferation. Vanillyl-derivatives of anandamide, such as olvanil and arvanil, exhibit even higher anti-proliferative activity. These effects are due to suppression of the levels of the 100 kDa prolactin receptor or of the high affinity NGF receptors (trk), are mediated by CB(1)-like cannabinoid receptors, and are enhanced by other CFADs. Inhibition of adenylyl cyclase and activation of mitogen-activated protein kinase underlie the anti-mitogenic actions of AEA. The possibility that CFADs act as local inhibitors of the proliferation of human breast cancer is discussed here.

Publication Types:
Review
Review, Tutorial
PMID: 10785541 [PubMed - indexed for MEDLINE]

Eur J Pharmacol 2000 Jan 17;387(3):343-7 Related Articles, Books, LinkOut

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Relative involvement of cannabinoid CB(1) and CB(2) receptors in the Delta(9)-tetrahydrocannabinol-induced inhibition of natural killer activity.

Massi P, Fuzio D, Vigano D, Sacerdote P, Parolaro D.
Department of Pharmacology, Chemotherapy and Toxicology, University of Milan, Via Vanvitelli 32/A, 20129, Milan, Italy.

We demonstrated that in vivo administration of Delta(9)-tetrahydrocannabinol in mice (15 mg/kg s.c.) significantly inhibited natural killer cell (NK) cytolytic

activity without affecting Concanavalin A (ConA)-induced splenocyte proliferation. Moreover, we investigated the effect of in vivo pretreatment with cannabinoid receptor antagonists, namely, the selective cannabinoid CB(1) receptor antagonist SR 141716 [N-piperidin-5-(4-chlorophenyl)-1-(2, 4-dichlorophenyl)-4-methyl-3-pyrazolecarboxamide] and the selective cannabinoid CB(2) receptor antagonist SR 144528 inverted question markN-[(1S)-endo-1,3, 3-trimethyl bicyclo [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazo le- 3-carboxamide inverted question mark, on Delta(9)-tetrahydrocannabinol-induced inhibition of NK cytolytic activity. Both antagonists partially reversed the Delta(9)-tetrahydrocannabinol inhibition of NK cytolytic activity, although the cannabinoid CB(1) receptor antagonist was more effective than the cannabinoid CB(2) receptor antagonist. The parallel measurement of interferon gamma and interleukin 2 levels revealed that Delta(9)-tetrahydrocannabinol significantly reduced (about 70%) the former cytokine without affecting the latter. Cannabinoid CB(1) and CB(2) receptor antagonists completely reversed the interferon gamma reduction induced by Delta(9)-tetrahydrocannabinol. Our results indicate that both types of cannabinoid receptors are involved in the complex network mediating NK cytolytic activity.
PMID: 10650181 [PubMed - indexed for MEDLINE]

Arch Pharm Res 1998 Jun;21(3):353-6 Related Articles, Books, LinkOut

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Boron trifluoride etherate on silica-A modified Lewis acid reagent (VII). Antitumor activity of cannabigerol against human oral epitheloid carcinoma cells.

Baek SH, Kim YO, Kwag JS, Choi KE, Jung WY, Han DS.
Department of Chemistry, Wonkwang University, Iksan, Korea.

Geraniol (1), olivetol (2), cannabinoids (3 and 4) and 5-fluorouracil (5) were tested for their growth inhibitory effects against human oral epitheloid carcinoma cell lines (KB) and NIH 3T3 fibroblasts using two different 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2H-tetrazolium bromide (MTT) assay and sulforhodamine B protein (SRB) assay. Cannabigerol (3) exhibited the highest growth-inhibitory activity against the cancer cell lines.
PMID: 9875457 [PubMed - indexed for MEDLINE]

Proc Soc Exp Biol Med 1995 Oct;210(1):64-76 Related Articles, Books, LinkOut

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Differential inhibition of RAW264.7 macrophage tumoricidal activity by delta 9tetrahydrocannabinol.

Burnette-Curley D, Cabral GA.
Department of Microbiology and Immunology, Virginia Commonwealth University/Medical College of Virginia, Richmond 23298-0678, USA.

delta 9tetrahydrocannabinol (THC), the major psychoactive component of

marijuana, has been shown to inhibit macrophage cell contact-dependent cytolysis of tumor cells. The purpose of this study was to determine whether THC inhibited macrophage cytolytic function by targeting selectively tumor necrosis factor (TNF)-dependent pathways versus L-arginine-dependent reactive nitrogen intermediates. An in vitro system employing RAW264.7 macrophage-like cells as effectors and TNF-sensitive mouse L929 fibroblasts or nitric oxide (NO.)-sensitive P815 mastocytoma cells as targets, was employed to assess the effect of THC on cytolysis. Macrophages were pretreated with THC or vehicle for 48 hr, subjected to multistep activation with 10 U/ml recombinant mouse gamma-interferon (IFN-gamma) plus 100 ng/ml LPS or to direct activation with 1 microgram/ml LPS, and co-cultured with tumor cells in the presence or absence of THC. THC inhibited TNF-dependent killing by macrophages subjected to either multistep or direct activation. Decreased amounts of TNF-alpha were detected in medium of macrophage cultures treated with THC. In contrast, THC inhibited NO.-dependent cell contact killing only for macrophages subjected to direct activation. Decreased levels of NO2-, a stable degradation product of the short-lived and highly toxic effector molecule NO., were produced by these macrophages. In addition, the effect of the enantiomeric pairs (-)CP55,940/(+)CP56,667 or (-)HU-210/(+)HU-211 on macrophage cell contact-dependent killing was assessed. Inhibition of macrophage tumoricidal activity against TNF-sensitive L929 cells was effected by both isomers of THC analogs. In contrast, both of the enantiomeric pairs had an effect on killing of NO.-sensitive P815 mastocytoma cells only for macrophages subjected to direct activation. These data suggest that cannabinoids inhibit macrophage cell contact-dependent killing of tumor cells by a noncannabinoid receptor-mediated mechanism. However, specific cytolytic pathways are inhibited differentially by cannabinoids depending on the activation stimuli to which macrophages are exposed.
PMID: 7675800 [PubMed - indexed for MEDLINE]

: J Natl Cancer Inst 1975 Sep;55(3):597-602

Antineoplastic activity of cannabinoid

Munson AE, Harris LS, Friedman MA, Dewey WL, Carchman RA.

Lewis lung adenocarcinoma growth was retarded by the oral administration of delta9-tetrahydrocannabinol (delta9-THC), delta8-tetrahydrocannabinol (delta8-THC), and cannabinol (CBN), but not cannabidiol (CBD). Animals treated for 10 consecutive days with delta9-THC, beginning the day after tumor implantation, demonstrated a dose-dependent action of retarded tumor growth. Mice treated for 20 consecutive days with delta8-THC and CBN had reduced primary tumor size. CBD showed no inhibitory effect on tumor growth at 14, 21, or 28 days. Delta9-THC, delta8-THC, and CBN increased the mean survival time (36% at 100 mg/kg, 25% at 200 mg/kg, and 27% at 50 mg/kg, respectively), whereas CBD did not. Delta9-THC administered orally daily until death in doses of 50, 100, or 200 mg/kg did not increase the life-spans of (C57BL/6 times DBA/2)F1 (BDF1) mice hosting the L1210 murine leukemia. However, delta9-THC administered daily for 10 days significantly inhibited

Friend leukemia virus-induced splenomegaly by 71% at 200 mg/kg as compared to 90.2% for actinomycin D. Experiments with bone marrow and isolated Lewis lung cells incubated in vitro with delta9-THC and delta8-THC showed a dose-dependent (10(-4)-10(-7)) inhibition (80-20%, respectively) of tritiated thymidine and 14C-uridine uptake into these cells. CBD was active only in high concentrations (10(-4)).
PMID: 1159836 [PubMed - indexed for MEDLINE]

Cancer Res 1976 Jan;36(1):95-100 Related Articles, Books, LinkOut

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The inhibition of DNA synthesis by cannabinoids.

Carchman RA, Harris LS, Munson AE.

Several of the cannabinoids found in marihuana have been shown to inhibit tumor growth and increase the life-span of mice bearing the Lewis lung adenocarcinoma. When trypsin-dispersed isolated Lewis lung cells are incubated in vitro, they maintain their capacity to carry out macromolecular synthesis (RNA, DNA, protein). This process can be inhibited by cytosine arabinoside, actinomycin D, or methyl-1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, whereas cyclophosphamide, an agent that must be bioactivated, was inactive. Inhibition of DNA synthesis as measured by [3H]thymidine uptake into acid-insoluble material was used as an index of cannabinoid activity against isolated Lewis lung cells, L1210 leukemia cells, and bone marrow cells incubated in vitro delta9-, delta8-, 1-hydroxy-3-n pentyl-, and 1-delta8-tetrahydrocannabinol, and cannabinol demonstrated a dose-dependent inhibition of DNA synthesis whereas cannabidiol and 1-hydroxy-3-n-pentylcannabidiol were markedly less inhibitory in our in vitro cell systems. Furthermore, our in vitro observations with these cannabinoids are supported by in vivo tumor inhibition studies. Ring modifications as in cannabichromene or cannabicyclol abolish in vitro activity as does dihydroxylation at the 8beta and 11 positions of 1-delta9-trans-tetrahydrocannabinol. Delta9-trans-tetrahydrocannabinol demonstrated the least toxicity of all inhibitory cannabinoids in vivo; this is supported by its lesser effect on bone marrow DNA synthesis in vitro.
PMID: 1248011 [PubMed - indexed for MEDLINE]

Res Commun Chem Pathol Pharmacol 1977 Aug;17(4):703-14 Related Articles, Books, LinkOut

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Effects of cannabinoids on L1210 murine leukemia. 1. Inhibition of DNA synthesis.

Tucker AN, Friedman MA.

The effect of cannabinoid derivatives on thymidine-3H uptake in L1210 murine leukemia was determined. In experiments at 200 mg/kg 3 hrs after treatment, the order of activity was delta9-tetrahydrocannabinol less than cannabinol less

than cannabidiol less than abnormal cannabidiol less than 11-hydroxy-delta9-tetrahydrocannabinol less than delta8-tetrahydrocannabinol. The inhibitory effect of delta8-tetrahydrocannabinol was 99%. When animals were dosed on consecutive days with delta9-tetrahydrocannabinol and killed on the third day, thymidine-3H incorporation was increased while delta8-tetrahydrocannabinol retained its inhibitory activity under the same conditions. Delta-9-tetrahydrocannabinol and delta8-tetrahydrocannabinol inhibited RNA and protein synthesis in a fashion analagous to the inhibition of DNA synthesis.
PMID: 897352 [PubMed - indexed for MEDLINE]

Cancer Biochem Biophys 1977;2(2):51-4 Related Articles, Books, LinkOut

In vivo effects of cannabinoids on macromolecular biosynthesis in Lewis lung carcinomas.

Friedman MA.

Cannabinoids represent a novel class of drugs active in increasing the life span mice carrying Lewis lung tumors and decreasing primary tumor size. In the present studies, the effects of delta9-THC, delta8-THC, and cannabidiol on tumor macromolecular biosynthesis were studied. These drugs inhibit thymidine-3H incorporation into DNA acutely, but did not inhibit leucine uptake into tumor protein. At 24 h after treatment, cannabinoids did not inhibit thymidine-3H incorporation into DNA, leucine-3H uptake into protein or cytidine-3H into RNA.
PMID: 616322 [PubMed - indexed for MEDLINE]

: J Natl Cancer Inst 1976 Mar;56(3):655-8 Related Articles, Books, LinkOut

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Effects of delta9-tetrahydrocannabinol in Lewis lung adenocarcinoma cells in tissue culture.

White AC, Munson JA, Munson AE, Carchman RA.

We found a dose-related decrease in DNA synthesis in transformed cell cultures treated with delta9-tetrahydrocannabinol (delta9-THC). The decrease, observed over a 4-hour period, was not accompanied by a change in the radioactive precursor pool as compared to that of control culture. The distribution of labeled products clearly differed from that observed after treatment with cytosine arabinoside. delta9-THC inhibited DNA synthesis at some point beyond the uptake of 3H-thymidine.
PMID: 943561 [PubMed - indexed for MEDLINE]

Prostaglandins Leukot Essent Fatty Acids 2002 Feb;66(2-3):319-32 Related Articles, Books, LinkOut

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Endocannabinoids in the immune system and cancer.

Parolaro D, Massi P, Rubino T, Monti E.
Department of Structural and Functional Biology, Pharmacology Unit, University of Insubria, Via A. Da Giussano 10, Busto Arsizio (Varese), 21052, Italy

The present review focuses on the role of the endogenous cannabinoid system in the modulation of immune response and control of cancer cell proliferation. The involvement of cannabinoid receptors, endogenous ligands and enzymes for their biosynthesis and degradation, as well as of cannabinoid receptor-independent events is discussed. The picture arising from the recent literature appears very complex, indicating that the effects elicited by the stimulation of the endocannabinoid system are strictly dependent on the specific compounds and cell types considered. Both the endocannabinoid anandamide and its congener palmitoylethanolamide, exert a negative action in the onset of a variety of parameters of the immune response. However, 2-arachidonoylglycerol appears to be the true endogenous ligand for peripheral cannabinoid receptors, although its action as an immunomodulatory molecule requires further characterization. Modulation of the endocannabinoid system interferes with cancer cell proliferation either by inhibiting mitogenic autocrine/paracrine loops or by directly inducing apoptosis; however, the proapoptotic effect of anandamide is not shared by other endocannabinoids and suggests the involvement of non-cannabinoid receptors, namely the VR1 class of vanilloid receptors. In conclusion, further investigations are needed to elucidate the function of endocannabinoids as immunosuppressant and antiproliferative/cytotoxic agents. The experimental evidence reviewed in this article argues in favor of the therapeutic potential of these compounds in immune disorders and cancer.
PMID: 12052046 [PubMed - in process]

J Pharmacol Exp Ther 2001 Dec;299(3):951-9 Related Articles, Books, LinkOut

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Inhibition of rat C6 glioma cell proliferation by endogenous and synthetic cannabinoids. Relative involvement of cannabinoid and vanilloid receptors.

Jacobsson SO, Wallin T, Fowler CJ.
Department of Pharmacology and Clinical Neuroscience, Umea University, Umea, Sweden.

The effects of the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG) upon rat C6 glioma cell proliferation were examined and compared with a series of synthetic cannabinoids and related compounds. Cells were treated with the compounds each day and cell proliferation was monitored for up to 5 days of exposure. AEA time- and concentration-dependently inhibited C6 cell proliferation. After 4 days of treatment, AEA and 2-AG inhibited C6 cell proliferation with similar potencies (IC(50) values of 1.6 and 1.8 microM, respectively), whereas palmitoylethanolamide showed no significant antiproliferative effects at concentrations up to 10 microM. The antiproliferative effects of both AEA and

2-AG were blocked completely by a combination of antagonists at cannabinoid receptors (SR141716A and SR144528 or AM251 and AM630) and vanilloid receptors (capsazepine) as well as by alpha-tocopherol (0.1 and 10 microM), and reduced by calpeptin (10 microM) and fumonisin B(1) (10 microM), but not by L-cycloserine (1 and 100 microM). CP 55,940, JW015, olvanil, and arachidonoyl-serotonin were all found to affect C6 glioma cell proliferation (IC(50) values of 5.6, 3.2, 5.5, and 1.6 microM, respectively), but the inhibition could not be blocked by cannabinoid + vanilloid receptor antagonists. It is concluded that the antiproliferative effects of the endocannabinoids upon C6 cells are brought about by a mechanism involving combined activation of both vanilloid receptors and to a lesser extent cannabinoid receptors, and leading to oxidative stress and calpain activation. However, there is at present no obvious universal mechanism whereby plant-derived, synthetic, and endogenous cannabinoids affect cell viability and proliferation.
PMID: 11714882 [PubMed - indexed for MEDLINE]

Proc Natl Acad Sci U S A 1998 Jul 7;95(14):8375-80 Related Articles, Free in PMC, Books, LinkOut

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The endogenous cannabinoid anandamide inhibits human breast cancer cell proliferation.

De Petrocellis L, Melck D, Palmisano A, Bisogno T, Laezza C, Bifulco M, Di Marzo V.
Istituto di Cibernetica, Consiglio Nazionale delle Ricerche), Consiglio Nazionale delle Ricerche, Via Toiano 6, 80072 Arco Felice, Naples, Italy.

Anandamide was the first brain metabolite shown to act as a ligand of "central" CB1 cannabinoid receptors. Here we report that the endogenous cannabinoid potently and selectively inhibits the proliferation of human breast cancer cells in vitro. Anandamide dose-dependently inhibited the proliferation of MCF-7 and EFM-19 cells with IC50 values between 0.5 and 1.5 microM and 83-92% maximal inhibition at 5-10 microM. The proliferation of several other nonmammary tumoral cell lines was not affected by 10 microM anandamide. The anti-proliferative effect of anandamide was not due to toxicity or to apoptosis of cells but was accompanied by a reduction of cells in the S phase of the cell cycle. A stable analogue of anandamide (R)-methanandamide, another endogenous cannabinoid, 2-arachidonoylglycerol, and the synthetic cannabinoid HU-210 also inhibited EFM-19 cell proliferation, whereas arachidonic acid was much less effective. These cannabimimetic substances displaced the binding of the selective cannabinoid agonist [3H]CP 55, 940 to EFM-19 membranes with an order of potency identical to that observed for the inhibition of EFM-19 cell proliferation. Moreover, anandamide cytostatic effect was inhibited by the selective CB1 receptor antagonist SR 141716A. Cell proliferation was arrested by a prolactin mAb and enhanced by exogenous human prolactin, whose mitogenic action was reverted by very low (0.1-0.5 microM) doses of anandamide. Anandamide suppressed the levels of the long form of the prolactin receptor in both EFM-19 and MCF-7 cells, as well as a

typical prolactin-induced response, i.e., the expression of the breast cancer cell susceptibility gene brca1. These data suggest that anandamide blocks human breast cancer cell proliferation through CB1-like receptor-mediated inhibition of endogenous prolactin action at the level of prolactin receptor.
PMID: 9653194 [PubMed - indexed for MEDLINE]

: Chem Phys Lipids 2000 Nov;108(1-2):191-209 Related Articles, Books, LinkOut

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Endocannabinoids and fatty acid amides in cancer, inflammation and related disorders.

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The long history of the medicinal use of Cannabis sativa and, more recently, of its chemical constituents, the cannabinoids, suggests that also the endogenous ligands of cannabinoid receptors, the endocannabinoids, and, particularly, their derivatives may be used as therapeutic agents. Studies aimed at correlating the tissue and body fluid levels of endogenous cannabinoid-like molecules with pathological conditions have been started and may lead to identify those diseases that can be alleviated by drugs that either mimic or antagonize the action of these substances, or modulate their biosynthesis and degradation. Hints for the therapeutic applications of endocannabinoids, however, can be obtained also from our previous knowledge of marijuana medicinal properties. In this article, we discuss the anti-tumor and anti-inflammatory activity of: (1) the endocannabinoids anandamide (arachidonoylethanolamide) and 2-arachidonoyl glycerol; (2) the bioactive fatty acid amides palmitoylethanolamide and oleamide; and (3) some synthetic derivatives of these compounds, such as the N-acyl-vanillyl-amines. Furthermore, the possible role of cannabimimetic fatty acid derivatives in the pathological consequences of cancer and inflammation, such as cachexia, wasting syndrome, chronic pain and local vasodilation, will be examined
Publication Types:
Review
Review, Academic
PMID: 11106791 [PubMed - indexed for MEDLINE]

Endocrinology 2000 Jan;141(1):118-26 Related Articles, Books, LinkOut

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Suppression of nerve growth factor Trk receptors and prolactin receptors by endocannabinoids leads to inhibition of human breast and prostate cancer cell proliferation.

Melck D, De Petrocellis L, Orlando P, Bisogno T, Laezza C, Bifulco M, Di Marzo V.
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delle Ricerche, Arco Felice (NA), Italy.

Anandamide and 2-arachidonoylglycerol (2-AG), two endogenous ligands of the CB1 and CB2 cannabinoid receptor subtypes, inhibit the proliferation of PRL-responsive human breast cancer cells (HBCCs) through down-regulation of the long form of the PRL receptor (PRLr). Here we report that 1) anandamide and 2-AG inhibit the nerve growth factor (NGF)-induced proliferation of HBCCs through suppression of the levels of NGF Trk receptors; 2) inhibition of PRLr levels results in inhibition of the proliferation of other PRL-responsive cells, the prostate cancer DU-145 cell line; and 3) CB1-like cannabinoid receptors are expressed in HBCCs and DU-145 cells and mediate the inhibition of cell proliferation and Trk/PRLr expression. Beta-NGF-induced HBCC proliferation was potently inhibited (IC50 = 50-600 nM) by the synthetic cannabinoid HU-210, 2-AG, anandamide, and its metabolically stable analogs, but not by the anandamide congener, palmitoylethanolamide, or the selective agonist of CB2 cannabinoid receptors, BML-190. The effect of anandamide was blocked by the CB1 receptor antagonist, SR141716A, but not by the CB2 receptor antagonist, SR144528. Anandamide and HU-210 exerted a strong inhibition of the levels of NGF Trk receptors as detected by Western immunoblotting; this effect was reversed by SR141716A. When induced by exogenous PRL, the proliferation of prostate DU-145 cells was potently inhibited (IC50 = 100-300 nM) by anandamide, 2-AG, and HU-210. Anandamide also down-regulated the levels of PRLr in DU-145 cells. SR141716A attenuated these two effects of anandamide. HBCCs and DU-145 cells were shown to contain 1) transcripts for CB1 and, to a lesser extent, CB2 cannabinoid receptors, 2) specific binding sites for [3H]SR141716A that could be displaced by anandamide, and 3) a CB1 receptor-immunoreactive protein. These findings suggest that endogenous cannabinoids and CB1 receptor agonists are potential negative effectors of PRL- and NGF-induced biological responses, at least in some cancer cells.
PMID: 10614630 [PubMed - indexed for MEDLINE]

Eur J Biochem 1998 Jun 15;254(3):634-42

Biosynthesis and degradation of bioactive fatty acid amides in human breast cancer and rat pheochromocytoma cells--implications for cell proliferation and differentiation.

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The endogenous cannabinoid, anandamide (arachidonoylethanolamide), and the sleep-inducing factor, oleamide (cis-9-octadecenoamide), represent two classes of long-chain fatty acid amides with several neuronal actions and metabolic pathways in common. Here we report that these two compounds are present in human breast carcinoma EFM-19 cells and rat adrenal pheochromocytoma PC-12 cells, together with the enzyme responsible for their degradation, fatty acid amide hydrolase, and the proposed biosynthetic

precursors for arachidonoylethanolamide and related acylethanolamides, the N-acyl-phosphatidylethanolamines. Lipids extracted from cells labelled with [14C]ethanolamine contained radioactive compounds with the same chromatographic behaviour as arachidonoylethanolamide and acyl-PtdEtns. The levels of these compounds were not influenced by either stimulation with ionomycin in EFM-19 cells or two-week treatment with the nerve growth factor in PC-12 cells. The chemical nature of arachidonoylethanolamide, related acylethanolamides and the corresponding acyl-PtdEtns was confirmed by gas chromatographic/mass spectrometric analyses of the purified compounds, which also showed the presence of higher levels of oleamide. The latter compound, which does not activate the central CB1 cannabinoid receptor, exhibited an anti-proliferative action on EFM-19 cells at higher concentrations than arachidonoylethanolamide (IC50 = 11.3 microM for oleamide and 2.1 microM for arachidonoylethanolamide), while at a low, inactive dose it potentiated an arachidonoylethanolamide cytostatic effect. The CB1 receptor selective antagonist SR 141716A (0.5 microM) reversed the effect of both arachidonoylethanolamide and oleamide. EFM-19 cells and PC-12 cells were found to contain a membrane-bound [14C]arachidonoylethanolamide-hydrolysing activity with pH dependency and sensitivity to inhibitors similar to those previously reported for fatty acid amide hydrolase. This enzyme was inhibited by oleamide in both intact cells and cell-free preparations. The presence of transcripts of fatty acid amide hydrolase in these cells was shown by northern blot analyses of their total RNA. The rate of [14C]arachidonoylethanolamide hydrolysis by intact cells, the kinetic parameters of arachidonoylethanolamide enzymatic hydrolysis and the amounts of the fatty acid amide hydrolase transcript, were not significantly influenced by a two-week treatment with nerve growth factor and subsequent transformation of PC-12 cells into neuron-like cells. These data show for the first time that: (a) induction by nerve growth factor of a sympathetic neuronal phenotype in PC-12 cells has no effect on arachidonoylethanolamide/oleamide metabolism, (b) arachidonoylethanolamide and oleamide are autacoid suppressors of human breast cancer cell proliferation. Moreover these data lend conclusive support to the previous hypothesis that oleamide may act as an enhancer of arachidonoylethanolamide actions through competitive inhibition of its degradation.
PMID: 9688276 [PubMed - indexed for MEDLINE]

Fundam Appl Toxicol 1996 Mar;30(1):109-17

Toxicity and carcinogenicity of delta 9-tetrahydrocannabinol in Fischer rats and B6C3F1 mice.

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delta 9-Tetrahydrocannabinol (delta 9-THC) was studied for potential carcinogenicity in rodents because it is the principal psychoactive ingredient in marihuana and it has potential medicinal uses. delta 9-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, 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. delta 9-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 delta 9-THC was carcinogenic in rats or mice.
PMID: 8812248 [PubMed - indexed for MEDLINE]

J Mol Med 2001;78(11):613-25Related Articles, Books, LinkOut

Control of the cell survival/death decision by cannabinoids.

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Cannabinoids, the active components of Cannabis sativa (marijuana), and their derivatives produce a wide spectrum of central and peripheral effects, some of which may have clinical application. The discovery of specific cannabinoid receptors and a family of endogenous ligands of those receptors has attracted much attention to cannabinoids in recent years. One of the most exciting and promising areas of current cannabinoid research is the ability of these compounds to control the cell survival/death decision. Thus cannabinoids may induce proliferation, growth arrest, or apoptosis in a number of cells, including neurons, lymphocytes, and various transformed neural and nonneural cells. The variation in drug effects may depend on experimental factors such as drug concentration, timing of drug delivery, and type of cell examined. Regarding the central nervous system, most of the experimental evidence indicates that cannabinoids may protect neurons from toxic insults such as glutamaergic overstimulation, ischemia and oxidative damage. In contrast, cannabinoids induce apoptosis of glioma cells in culture and regression of malignant gliomas in vivo. Breast and prostate cancer cells

are also sensitive to cannabinoid-induced antiproliferation. Regarding the immune system, low doses of cannabinoids may enhance cell proliferation, whereas high doses of cannabinoids usually induce growth arrest or apoptosis. The neuroprotective effect of cannabinoids may have potential clinical relevance for the treatment of neurodegenerative disorders such as multiple sclerosis, Parkinson's disease, and ischemia/stroke, whereas their growth-inhibiting action on transformed cells might be useful for the management of malignant brain tumors. Ongoing investigation is in search for cannabinoid-based therapeutic strategies devoid of nondesired psychotropic effects.
Publication Types:
Review
Review, Academic
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1: Cancer Causes Control 1997 Sep;8(5):722-8 Related Articles, Books, LinkOut

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Cannabinoids Halt Pancreatic Cancer, Breast Cancer Growth, Studies Say.

Madrid, Spain: Compounds in cannabis inhibit cancer cell growth in human breast cancer cell lines and in pancreatic tumor cell lines, according to a pair of preclinical trials published in the July issue of the journal of the American Association for Cancer Research.

In one trial, investigators at Complutense University in Spain and the Institut National de la Sante et de la Recherche Medicale (INSERM) in France assessed the anti-cancer activity of cannabinoids in pancreatic cancer cell lines and in animals. Cannabinoid administration selectively increased apoptosis (programmed cell death) in pancreatic tumor cells while ignoring healthy cells, researchers found. In addition, "cannabinoid treatment inhibited the spreading of pancreatic tumor cells ... and reduced the growth of tumor cells" in animals.

"These findings may contribute to ... a new therapeutic approach for the treatment of pancreatic cancer," authors concluded.

In the second trial, investigators at Spain's Complutense University reported that THC administration "reduces human breast cancer cell proliferation [in vitro] by blocking the progression of the cell cycle and by inducing apoptosis." Authors concluded that their findings "may set the bases for a cannabinoid therapy for the management of breast cancer."

Previous preclinical data published in May in the Journal of Pharmacological and Experimental Therapeutics reported that non-psychoactive cannabinoids, particularly cannabidiol (CBD), dramatically halt the spread of breast cancer cells and recommended their use in cancer therapy.

Separate trials have also shown cannabinoids to reduce the size and halt the spread of glioma (brain tumor) cells in animals and humans in a dose dependent manner.

Additional preclinical studies have demonstrated cannabinoids to inhibit cancer cell growth and selectively trigger malignant cell death in skin_cancer_cells, leukemic_cells, lung cancer cells, and prostate_carcinoma_cells, among other cancerous cell lines.

For more information, please contact Paul Armentano, NORML Senior Policy Analyst, at (202) 483-5500. Full text of both studies, "Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes" and "Delta-9-tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation" are available in the July 1, 2006 issue of Cancer Research, available online at: http://cancerres.aacrjournals.org/

Additional information on cannabinoids' anti-cancer properties is available in NORML's report, "Cannabinoids as Cancer Hope," online at: www.norml.org/index.cfm?Group_ID=6814

Further Reading

- Combining Components of Marijuana Enhances Inhibitory Effects on Brain Cancer
- Cannabis chemicals may help fight prostate cancer
- Marijuana Compound May Fight Lung Cancer
- Study: Pot slows lung cancer in mice
- Cannabidiol Dramatically Inhibits Breast Cancer Cell Growth, Study Says
- Five Scientific Journals Published Prominent Articles
- Pot Shrinks Tumors; Government Knew In '74 , San Antonio Current (TX), Thu, 29 Mar 2001
- GW Pharmaceuticals Anti-Tumor Effects