National Cancer Institute
at the National Institutes of Health

Cannabis and Cannabinoids (PDQ®)

Laboratory/Animal/Preclinical Studies

Cannabinoids are a group of 21 carbon terpenophenolic compounds produced uniquely by Cannabis sativa and Cannabis indica species.[1,2] These plant-derived compounds may be referred to as phytocannabinoids. Although delta-9-tetrahydrocannabinol (THC) is the primary psychoactive ingredient, other known compounds with biologic activity are cannabinol, cannabidiol, cannabichromene, cannabigerol, tetrahydrocannabivirin, and delta-8-THC. Cannabidiol, in particular, is thought to have significant analgesic and anti-inflammatory activity without the psychoactive effect (high) of delta-9-THC.

Antitumor Effects

One study in mice and rats suggested that cannabinoids may have a protective effect against the development of certain types of tumors. [3] During this 2-year study, groups of mice and rats were given various doses of THC by gavage. A dose-related decrease in the incidence of hepatic adenoma tumors and hepatocellular carcinoma was observed in the mice. Decreased incidences of benign tumors (polyps and adenomas) in other organs (mammary gland, uterus, pituitary, testis, and pancreas) were also noted in the rats. In another study, delta-9-THC, delta-8-THC, and cannabinol were found to inhibit the growth of Lewis lung adenocarcinoma cells *in vitro* and *in vivo* .[4] In addition, other tumors have been shown to be sensitive to cannabinoid-induced growth inhibition. [5-8]

Cannabinoids may cause antitumor effects by various mechanisms, including induction of cell death, inhibition of cell growth, and inhibition of tumor angiogenesis and metastasis. [9-11] Cannabinoids appear to kill tumor cells but do not affect their nontransformed counterparts and may even protect them from cell death. These compounds have been shown to induce apoptosis in glioma cells in culture and induce regression of glioma tumors in mice and rats. Cannabinoids protect normal glial cells of astroglial and oligodendroglial lineages from apoptosis mediated by the CB1 receptor. [10,11]

In an *in vivo* model using severe combined immunodeficient mice, subcutaneous tumors were generated by inoculating the animals with cells from human non-small cell lung carcinoma cell lines.[12] Tumor growth was inhibited by 60% in THC-treated mice compared with vehicle-treated control mice. Tumor specimens revealed that THC had antiangiogenic and antiproliferative effects.

In addition, both plant-derived and endogenous cannabinoids have been studied for anti-inflammatory effects. A mouse study demonstrated that endogenous cannabinoid system signaling is likely to provide intrinsic protection against colonic inflammation. [13] As a result, a hypothesis that phytocannabinoids and endocannabinoids may be useful in the prevention and treatment of colorectal cancer has been developed.[14]

Another study has shown delta-9-THC is a potent and selective antiviral agent against Kaposi

sarcoma-associated herpesvirus (KSHV), also known as human herpesvirus 8.[15] The researchers concluded that additional studies on cannabinoids and herpesviruses are warranted, as they may lead to the development of drugs that inhibit the reactivation of these oncogenic viruses. Subsequently, another group of investigators reported increased efficiency of KSHV infection of human dermal microvascular epithelial cells in the presence of low doses of delta-9-THC.[16]

Appetite Stimulation

Many animal studies have previously demonstrated that delta-9-THC and other cannabinoids have a stimulatory effect on appetite and increase food intake. It is believed that the endogenous cannabinoid system may serve as a regulator of feeding behavior. The endogenous cannabinoid anandamide potently enhances appetite in mice.[17] Moreover, CB1 receptors in the hypothalamus may be involved in the motivational or reward aspects of eating.[18]

Analgesia

Understanding the mechanism of cannabinoid-induced analgesia has been increased through the study of cannabinoid receptors, endocannabinoids, and synthetic agonists and antagonists. The CB1 receptor is found in both the central nervous system (CNS) and in peripheral nerve terminals. Similar to opioid receptors, increased levels of the CB1 receptor are found in sections of the brain that regulate nociceptive processing.[19] CB2 receptors, located predominantly in peripheral tissue, exist at very low levels in the CNS. With the development of receptor-specific antagonists, additional information about the roles of the receptors and endogenous cannabinoids in the modulation of pain has been obtained.[20,21]

Cannabinoids may also contribute to pain modulation through an anti-inflammatory mechanism; a CB2 effect with cannabinoids acting on mast cell receptors to attenuate the release of inflammatory agents, such as histamine and serotonin, and on keratinocytes to enhance the release of analgesic opioids has been described.[22-24]

References

1. Adams IB, Martin BR: Cannabis: pharmacology and toxicology in animals and humans. Addiction 91 (11): 1585-614, 1996. [PUBMED Abstract]
2. Grotenhermen F, Russo E, eds.: Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential. Binghamton, NY: The Haworth Press, 2002.
3. National Toxicology Program .: NTP Toxicology and Carcinogenesis Studies of 1-Trans-Delta(9)-Tetrahydrocannabinol (CAS No. 1972-08-3) in F344 Rats and B6C3F1 Mice (Gavage Studies). Natl Toxicol Program Tech Rep Ser 446 (): 1-317, 1996. [PUBMED Abstract]
4. Bifulco M, Laezza C, Pisanti S, et al.: Cannabinoids and cancer: pros and cons of an antitumour strategy. Br J Pharmacol 148 (2): 123-35, 2006. [PUBMED Abstract]
5. Sánchez C, de Ceballos ML, Gomez del Pulgar T, et al.: Inhibition of glioma growth in vivo by selective activation of the CB(2) cannabinoid receptor. Cancer Res 61 (15): 5784-9, 2001. [PUBMED Abstract]
6. McKallip RJ, Lombard C, Fisher M, et al.: Targeting CB2 cannabinoid receptors as a novel therapy to treat malignant lymphoblastic disease. Blood 100 (2): 627-34, 2002. [PUBMED Abstract]
7. Casanova ML, Blázquez C, Martínez-Palacio J, et al.: Inhibition of skin tumor growth and angiogenesis in vivo by activation of cannabinoid receptors. J Clin Invest 111 (1): 43-50, 2003. [PUBMED Abstract]
8. Blázquez C, González-Feria L, Alvarez L, et al.: Cannabinoids inhibit the vascular endothelial growth factor pathway in gliomas. Cancer Res 64 (16): 5617-23, 2004.

[PUBMED Abstract]

9. Guzmán M: Cannabinoids: potential anticancer agents. Nat Rev Cancer 3 (10): 745-55, 2003. [PUBMED Abstract]

10. Blázquez C, Casanova ML, Planas A, et al.: Inhibition of tumor angiogenesis by cannabinoids. FASEB J 17 (3): 529-31, 2003. [PUBMED Abstract]

11. Vaccani A, Massi P, Colombo A, et al.: Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism. Br J Pharmacol 144 (8): 1032-6, 2005. [PUBMED Abstract]

12. Preet A, Ganju RK, Groopman JE: Delta9-Tetrahydrocannabinol inhibits epithelial growth factor-induced lung cancer cell migration in vitro as well as its growth and metastasis in vivo. Oncogene 27 (3): 339-46, 2008. [PUBMED Abstract]

13. Massa F, Marsicano G, Hermann H, et al.: The endogenous cannabinoid system protects against colonic inflammation. J Clin Invest 113 (8): 1202-9, 2004. [PUBMED Abstract]

14. Patsos HA, Hicks DJ, Greenhough A, et al.: Cannabinoids and cancer: potential for colorectal cancer therapy. Biochem Soc Trans 33 (Pt 4): 712-4, 2005. [PUBMED Abstract]

15. Medveczky MM, Sherwood TA, Klein TW, et al.: Delta-9 tetrahydrocannabinol (THC) inhibits lytic replication of gamma oncogenic herpesviruses in vitro. BMC Med 2: 34, 2004. [PUBMED Abstract]

16. Zhang X, Wang JF, Kunos G, et al.: Cannabinoid modulation of Kaposi's sarcoma-associated herpesvirus infection and transformation. Cancer Res 67 (15): 7230-7, 2007. [PUBMED Abstract]

17. Mechoulam R, Berry EM, Avraham Y, et al.: Endocannabinoids, feeding and suckling--from our perspective. Int J Obes (Lond) 30 (Suppl 1): S24-8, 2006. [PUBMED Abstract]

18. Fride E, Bregman T, Kirkham TC: Endocannabinoids and food intake: newborn suckling and appetite regulation in adulthood. Exp Biol Med (Maywood) 230 (4): 225-34, 2005. [PUBMED Abstract]

19. Walker JM, Hohmann AG, Martin WJ, et al.: The neurobiology of cannabinoid analgesia. Life Sci 65 (6-7): 665-73, 1999. [PUBMED Abstract]

20. Meng ID, Manning BH, Martin WJ, et al.: An analgesia circuit activated by cannabinoids. Nature 395 (6700): 381-3, 1998. [PUBMED Abstract]

21. Walker JM, Huang SM, Strangman NM, et al.: Pain modulation by release of the endogenous cannabinoid anandamide. Proc Natl Acad Sci U S A 96 (21): 12198-203, 1999. [PUBMED Abstract]

22. Facci L, Dal Toso R, Romanello S, et al.: Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. Proc Natl Acad Sci U S A 92 (8): 3376-80, 1995. [PUBMED Abstract]

23. Ibrahim MM, Porreca F, Lai J, et al.: CB2 cannabinoid receptor activation produces antinociception by stimulating peripheral release of endogenous opioids. Proc Natl Acad Sci U S A 102 (8): 3093-8, 2005. [PUBMED Abstract]

24. Richardson JD, Kilo S, Hargreaves KM: Cannabinoids reduce hyperalgesia and inflammation via interaction with peripheral CB1 receptors. Pain 75 (1): 111-9, 1998. [PUBMED Abstract]