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Cannabis and Cannabinoids (PDQ®)

Laboratory/Animal/Preclinical Studies

Cannabinoids are a group of 21-carbon–containing 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 (CBD), cannabichromene, cannabigerol, tetrahydrocannabivarin, and delta-8-THC. CBD, 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 invasion and metastasis.[9-12] One review summarizes the molecular mechanisms of action of cannabinoids as antitumor agents.[13] 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 gliomacells 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.[14]

The effects of delta-9-THC and a synthetic agonist of the CB2 receptor were investigated in hepatocellular carcinoma (HCC).[15] Both agents reduced the viability of hepatocellular carcinoma cells*in vitro* and demonstrated antitumor effects in hepatocellular carcinoma subcutaneous xenografts in nude mice. The investigations documented that the anti-HCC effects are mediated by way of the CB2 receptor. Similar to findings in glioma cells, the cannabinoids were shown to trigger cell death through stimulation of an endoplasmic reticulum stress pathway that activates autophagy

and promotes apoptosis. Other investigations have confirmed that CB1 and CB2 receptors may be potential targets innon-small cell lung carcinoma [16] and breast cancer.[17]

An *in vitro* study of the effect of CBD on programmed cell death in breast cancer cell lines found that CBD induced programmed cell death, independent of the CB1, CB2, or vanilloid receptors. CBD inhibited the survival of both estrogen receptor–positive and estrogen receptor–negative breast cancercell lines, inducing apoptosis in a concentration-dependent manner while having little effect on nontumorigenic, mammary cells.[18]

CBD has also been demonstrated to exert a chemopreventive effect in a mouse model of colon cancer.[19] In the experimental system, azoxymethane increased premalignant and malignant lesions in the mouse colon. Animals treated with azoxymethane and CBD concurrently were protected from developing premalignant and malignant lesions. In *in vitro* experiments involving colorectal cancer cell lines, the investigators found that CBD protected DNA from oxidative damage, increased endocannabinoid levels, and reduced cell proliferation.

Another investigation into the antitumor effects of CBD examined the role of intercellular adhesion molecule-1 (ICAM-1).[12] ICAM-1 expression has been reported to be negatively correlated with cancermetastasis. In lung cancer cell lines, CBD upregulated ICAM-1, leading to decreased cancer cell invasiveness.

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.[20] 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. However, research with immunocompetent murine tumor models has demonstrated immunosuppression and enhanced tumor growth in mice treated with THC.[21,22]

In addition, both plant-derived and endogenous cannabinoids have been studied for anti-inflammatoryeffects. A mouse study demonstrated that endogenous cannabinoid system signaling is likely to provide intrinsic protection against colonic inflammation.[23] As a result, a hypothesis that phytocannabinoids and endocannabinoids may be useful in the risk reduction and treatment of colorectal cancer has been developed.[24-27]

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.[28] Moreover, CB1 receptors in the hypothalamus may be involved in the motivational or reward aspects of eating.[29]

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 toopioid receptors, increased levels of the CB1 receptor are found in regions of the brain that regulate nociceptive processing.[30] 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.[31,32]

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.[33-35] One study reported that the efficacy of synthetic CB1- and CB2-receptor agonists were comparable with the efficacy of morphine in a murine model of tumor pain.[36]

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