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Mini-review

Cannabinoids: potential antitumoral agents?

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Abstract

Cannabinoids, the active components of *Cannabis sativa* L., act in the body by mimicking endogenous substances - the endocannabinoids - that activate specific cell surface receptors. Cannabinoids exert palliative effects in cancer patients. For example, they inhibit chemotherapy-induced nausea and vomiting, stimulate appetite and inhibit pain. In addition, cannabinoids inhibit tumor growth in laboratory animals. They do so by modulating key cell signaling pathways, thereby inducing antitumoral actions such as the apoptotic death of tumor cells as well as the inhibition of tumor angiogenesis. Of interest, cannabinoids seem to be selective antitumoral compounds as they can kill tumor cells without significantly affecting the viability of their non-transformed counterparts. On the basis of these preclinical findings a pilot clinical study of Δ^9-tetrahydrocannabinol (THC) in patients with recurrent glioblastoma multiforme has recently been run. The fair safety profile of THC, together with its possible growth-inhibiting action on tumor cells, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids.

Key words: cannabinoid, receptor, tumor, cancer, apoptosis, angiogenesis, experimental therapeutics, clinical trial.

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Preparations from the hemp plant *Cannabis sativa* L. have been used for many centuries both medicinally and recreationally. However, the chemical structure of their unique, active components — the cannabinoids — was not elucidated until the early 1960s. Although the pharmacology of most of the cannabinoids is still unknown, it is widely accepted that Δ^9-tetrahydrocannabinol (THC) is the most important, owing to its high potency and abundance in cannabis. Nowadays we know that THC exerts a wide variety of biological effects by mimicking endogenous substances - the so-called endocannabinoids - that bind to and activate specific cell surface cannabinoid receptors, two of which - CB_1 and CB_2 - have so far been cloned and well characterized from mammalian tissues [14, 18].

One of the most active areas of current research in the cannabinoid field is the study of the potential application of cannabinoids as therapeutic agents. Among these possible applications, cannabinoids have been known to exert palliative effects in cancer patients since the early 1970s [11, 13]. The best established of these effects is the inhibition of chemotherapy-induced nausea and vomiting. Today, capsules of THC (Marinol-TM) and its synthetic analogue nabilone (Cesamet-TM) are approved in several countries for that purpose. Other potential palliative effects of cannabinoids in oncology - supported by phase III clinical trials - include appetite stimulation and pain inhibition.

Cannabinoids have also been proposed as potential antitumoral agents on the basis of experiments performed both in cultured cells and in animal models of cancer [1, 11]. These antiproliferative properties of cannabis compounds were first reported by 30 years ago, when it was shown that THC inhibits lung adenocarcinoma cell growth in vitro and after oral administration in mice [16]. Although these observations were promising, further studies in this area were not performed until the late 1990s, mostly by Di Marzo's group (reviewed in [1]) and Guzmán's group (reviewed in [11]). A number of plant-derived, synthetic and endogenous cannabinoids are now known to exert antiproliferative actions on a wide spectrum of tumor cells in culture. More importantly, cannabinoid administration to mice curbs the growth of various types of tumor

xenografts, including lung carcinoma [16], glioma [10], thyroid epithelioma [2], skin [8] and pancreatic [6] carcinoma, lymphoma [17] and melanoma [3]. The requirement of cannabinoid receptors for this antitumoral effect has been revealed by various biochemical and pharmacological approaches, in particular by determining cannabinoid receptor expression in the tumors and by using selective cannabinoid receptor agonists and antagonists.

Most of our research on cannabinoid antitumoral action has focused on malignant brain tumors (gliomas), one of the most aggressive forms of cancer. Initial experiments showed that local administration of THC or the synthetic cannabinoid agonist WIN-55,212-2 reduces the size of tumors generated by intracranial inoculation of a glioma cell line in rats [10]. Additional studies were performed on tumor xenografts generated by subcutaneous injection of glioma cells in immune-deficient mice. Local administration of THC, WIN-55,212-2 or the selective CB_2 cannabinoid receptor agonist JWH-133 decreased the growth of tumors derived not only from a glioma cell line but also from glioblastoma multiforme cells obtained from a patient [10, 22]. These and other studies also showed that cannabinoids inhibit glioma cell growth by binding to their specific cannabinoid receptors on the surface of tumor cells, thereby modulating key cell signaling pathways. This reduces in turn the proliferation of tumor cells by at least two mechanisms: a process of programmed cell death called apoptosis [7, 10, 22] and an impairment of tumor vascularization and therefore blood (i.e., nutrient and oxygen) supply [4, 5, 8, 19]. Remarkably, this antiproliferative effect seems to be selective for tumor cells, as the survival of normal brain cells is unaffected or even favored by cannabinoid challenge [11], supporting the notion that cannabinoid receptors regulate cell survival and cell death pathways differently in tumor and non-tumor cells.

On the basis of these preclinical findings we have recently conducted a pilot phase I clinical trial in which 9 patients with recurrent glioblastoma multiforme were administered THC intratumorally [12]. The patients had previously failed standard therapy (surgery and radiotherapy) and had clear evidence of tumor progression. The primary endpoint of the study was to determine the safety of intracranial THC administration. We also evaluated THC action on length of survival and various tumor cell parameters. A dose escalation regime for THC administration was assessed. Cannabinoid delivery was safe (no significant alterations in physical, neurological, biochemical and haematological parameters could be ascribed to THC in any of the patients) and could be achieved without overt psychoactive effects. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% CI: 15-33). THC decreased tumor cell proliferation (as determined by Ki67 immunostaining; [12]) and increased tumor cell apoptosis (as determined by active-caspase 3 immunostaining; [7]) when administered to 2 patients.

The fair safety profile of THC, together with its possible antiproliferative action on tumor cells, may set the basis for future trials aimed at evaluating the potential antitumoral activity of cannabinoids. These possible new trials could involve one or more of the following modifications:

- *Patients with newly diagnosed tumors.* Pilot placebo-controlled trials for recurrent glioblastoma multiforme with temozolomide, a DNA-damaging agent that constitutes the current benchmark for the management of malignant gliomas, showed a very slight impact on overall length of survival (median survival = 24 weeks; 6-month survival = 46-60%) [9]. Further trials in patients with newly-diagnosed tumors allowed a clear improvement in the therapeutic efficacy of temozolomide through the development of various administration regimes [20, 23]. It is therefore conceivable that better outcomes could also be obtained with cannabinoid-based therapies in newly-diagnosed gliomas.

- *THC in combination with temozolomide.* Glioblastoma multiforme – particularly when relapse occurs - is an extremely lethal disease. The success of potential treatments is usually hampered by factors such as the rapid growth, remarkable heterogeneity, high degree of infiltration and extreme resistance to chemotherapy displayed by these tumors. It is therefore conceivable that combined therapies could provide better results than single-agent therapies. For example, by synergizing via complementary signaling pathways THC plus temozolomide might exert a more potent clinical impact than either THC or temozolomide alone.

- *Non-invasive administration route.* Although intratumoral delivery may allow a high local concentration of the drug in situ, in the case of large tumors such as actively growing recurrent glioblastoma multifome the local perfusion through a catheter placed at one point of the tumor constitutes an obvious limitation of the technique. In addition, a non-invasive, less traumatic route would be more desirable in the clinical practice. Alternative or complementary options for THC administration would include oral capsules and oro-mucosal sprays. These preparations could also include cannabidiol in their composition as this cannabinoid has been shown to inhibit the growth of glioma cell xenografts in nude mice [15] and may prevent some of the unwanted effects of THC treatment in patients [21].

- *Other types of tumors.* We and others have shown that THC and synthetic cannabinoids, besides their anti-glioma activity, inhibit the growth of different types of tumor xenografts in mice (see above). Trials on these and other types of tumors might also be

run to test the antitumoral activity of cannabinoids in these malignant diseases.

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