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Review Article

Cannabinoid Therapy for Glioblastoma Treatment: A Review

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Abstract

In recent years, studies have brought to light preclinical evidence of the ability of cannabinoids to reduce tumor growth in animal models, and clinical trials have been designed to study this activity in patients with glioblastoma. The data in animal models show promising results. So far it has been seen that the administration of THC is safe, and can be carried out without psychoactive effects. These molecules act through receptors coupled to the G protein, which are part of the endocannabinoid system and which have been called CB1 and CB2. THC can attenuate tumor progression in some patients, and appears to have a positive effect on survival, similar to that generated by other chemotherapeutic agents. More trials are needed to validate this antitumor action, both in combination with other therapies, and independently. At this time there is not enough scientific evidence to be able to conclusively affirm that cannabinoid treatment can contribute improve current therapies given to patients with brain tumors or other types of tumors.

Keywords: Glioblastoma; Endocannabinoid System; Antitumor Therapy

Introduction

The lack of satisfactory clinical results in the treatment of glioblastoma has led us to look for more effective therapies and with mechanisms of action different from the conventional ones. Cannabis-based products are emerging as an effective and safe therapeutic alternative. At present, cannabinoids are considered a complementary tool for the symptomatic management of different chronic neurological diseases, when other first-line therapies have failed. Current scientific evidence supports the use of cannabis-based products for the treatment of refractory epilepsy, chronic neuropathic pain, spasticity and bladder dysfunction associated with multiple sclerosis, some movement disorders such as tremor, dystonia or Tourette syndrome, headache and some sleep disorders related to neurological diseases [1].

For decades, the prescription of cannabinoids for therapeutic purposes has been restricted and controlled by specific regulatory frameworks, which has limited the development of clinical research, as well as the commercialization of cannabinoids for medicinal use. However, in recent years it has seen significant global progress that promotes the safe use and responsible prescription of medicinal cannabis in different clinical conditions. Perhaps one of the reasons why we still do not see these drugs in the clinic is due to the attempt to elucidate the molecular mechanisms that promote apoptosis, arrest in the G_0 mitosis phase, inhibition of angiogenesis and the possibility of the cell to metastasize [2].

Currently, we know that cannabis plants contain more than 100 terpenophenolic compounds, which have been called cannabinoids. Depending on their origin, three general types of cannabinoids are recognized: phytocannabinoids naturally synthesized by the cannabis plant; endogenous cannabinoids or endocannabinoids, produced naturally by animals and humans; and synthetic cannabinoids, similar compounds generated in the laboratory. The

2 most abundant are delta-9-tetrahydrocannabinol (Δ9-THC) and cannabidiol (CBD). In different preclinical models of epilepsy, it has been suggested that cannabinoids act in systems different from the endocannabinoid, opening the possibility of new therapeutic strategies and novel mechanisms of action. In recent years, some case reports have been published that have described a significant improvement in the control of glioblastoma with the use of different cannabis-based products. The great expectation that has been generated by these reports of isolated cases has begun to be confirmed through controlled and randomized clinical trials [3,4].

Although the results are promising, several studies have shown that CBD has complex pharmacokinetics, variable bioavailability and a high percentage of drug interactions, which is why different therapeutic and pharmacological alternatives have been sought. In this sense, some studies have used cannabis extracts enriched with CBD that usually evaluate CBD:THC at different ratios in different preclinical and pharmacological hypotheses that suggest that the associative effects of all the components of the plant are more effective than isolated chemicals. In some countries such as Israel, the efficacy of CBD-enriched cannabis extracts (CBD:THC ratio of 20:1) has been evaluated for the control of symptoms associated to glioblastoma like epilepsy, finding that more than 50% of patients achieve a significant improvement in the frequency of crises; additionally, a subjective improvement in behavior, alertness, communication and some motor skills has been reported [5].

Mechanism of action and pharmacological aspects

The mechanism of action, the pharmacokinetics and the pharmacodynamics of cannabinoids is complex. In the case of the antitumor actions of cannabinoids, we now know that they are also largely due to the ability to activate the CB1 and CB2 receptors present in tumor cells, which leads to a series of triggers within them that lead to their programmed death (or "apoptosis"). Recent studies indicate that THC activates apoptosis in tumor cells through a complex signaling pathway that leads to the stimulation of another cellular process called autophagy (literally self-digestion). On the other hand, it has also been discovered that, in addition to promoting the death of tumor cells, cannabinoids can help to block tumor growth by inhibiting tumor angiogenesis (a process by which the tumor is able to modify the blood vessels so that it can more easily obtain the nutrients and oxygen it needs to grow). Lastly, cannabinoids also inhibit the ability of tumor cells to migrate and invade other tissues [6].

Their antiangiogenic effect also contributes to the antitumor action of cannabinoids. A small group of affected genes in cannabinoid-treated tumors are directly or indirectly related to the VEGF pathway [7]. Cannabinoid treatment has been proven to be safe as:

- It is specific for transformed cells: not only does it not affect non-tumor cells, but it also protects them (effect mediated by the PI3K/Akt pathway), in addition to facilitating their generation and survival.

- It can be carried out without psychoactive side effects: The CB1 receptor, responsible for psychoactive effects is very abundant in the brain, and its levels vary very little in cancer, while the CB2 receptor, which does not mediate this type of effects, is expressed in cells of the immune system and glial cells, increasing their levels during tumor development. CB2 is a marker of glioma malignancy and a possible way to inhibit glioma growth without psychoactive effects.

It is important to determine the molecular basis of differential cannabinoid signaling in transformed and non-transformed cells.

It is known that in gliomas the binding of the cannabinoid to the receptor induces an increase in ceramide, which causes a decrease in Akt and therefore apoptosis. However, in normal astrocytes, the binding of the cannabinoid to the receptor causes an increase in Akt activity, and therefore induces cell survival. The analysis of the amount of ceramide present in the cells shows that while in tumor cells two ceramide peaks are generated, in non-transformed cells there is only the first one, there is no *de novo* synthesis of ceramide, therefore, it is this second ceramide peak responsible for the differential effect [8].

Some clinical trials are trying to clarify whether the effect of the cannabinoid THC, administered intracranially, can be effective in inhibiting growth in recurrent glioblastoma [9]. So far it has been seen that the administration of THC is safe, and can be carried out without psychoactive effects. THC can attenuate tumor progression in some patients, and appears to have a positive effect on survival, similar to that generated by other chemotherapeutic agents. More trials are needed to validate this antitumor action, both in combination with other therapies, and independently [10].

In the plasma membrane of tumor cells there are CB1 and CB2 receptors coupled to the generation of ceramide, a sphingolipid that induces apoptosis by two mechanisms [11,12]:

- Short-term: ceramides are generated from a membrane phospholipid precursor (sphingomyelin) substrate of a lipase activated by the cannabinoid receptor through the adapter protein FAN.
- Long-term: a second ceramide peak is generated by de novo synthesis from the amino acid serine and fatty acids.

Both ceramide peaks are coupled to different types of molecular targets, the long-term peak being the one involved in the induction of apoptosis. Among the intracellular targets of ceramide are the ERK and Akt kinases.

Cells resistant to cannabinoid apoptosis can be isolated from gliomas. Both the activation of the ceramide synthesis regulatory enzyme (SPT) and the ceramide levels of the cell are increased in cannabinoid-sensitive subclones, but not in those resistant to apoptosis. If the action of the SPT enzyme is blocked or the second ceramide generation peak is pharmacologically inhibited, the cell survives. And *vice versa*, if SPT is overexpressed or the long-term peak of ceramide is induced in resistant cells, the cells die [13].

The main mechanisms of action are [14]:

- The reduction in excitotoxicity is due to the modulation of glutamate release thanks to the presence of CB1 receptors at glutamatergic terminals.
- The antioxidant effect of cannabinoids is due to their molecular structure, acting as radical scavengers and thus reducing reactive oxygen species.
- The presence and activation of CB2 receptors located on microglia cells decreases the release of pro inflammatory mediators and increases survival factors. Additionally, the CB1 and CB2 receptors are located on the astrocyte membrane, also favoring survival processes, contributing to neuroprotection.
- CB1 and CB2 receptors are present on oligodendrocyte precursor cells (OPCs) and on neuron precursor cells (NPCs). Modulation through these receptors in these cells is associated with processes involved in remyelination and neurorepair. The vision of the future that arises is the ability to pharmacologically modulate these receptors to try to neurorepair and remyelinate injured areas.

Cannabis plants contain more than 100 phytocannabinoids and terpenes that act through molecular pathways and complex signaling networks. The 2 most abundant compounds in different cannabis plants, and also the ones that have been studied the most, are Δ9-THC and CBD [15]. These molecules act through receptors coupled to the G protein, which are part of the endocannabinoid system and which have been called CB1 (expressed mainly in neurons of the central and peripheral nervous system) and CB2 (expressed mainly in cells of the immune system). CB1 receptors decrease neuronal excitability and neurotransmitter release by modulating the opening of potassium channels and blocking calcium channels. CB2 receptors are involved in immune modulation. Δ9-THC is a partial agonist of CB1/CB2 receptors [16] and has a powerful anti-inflammatory effect, however, it is responsible for most of the psychotropic, cognitive and behavioral effects of cannabis; for this reason, little effort has been made to develop THC as an antiepileptic drug. Additionally, in some preclinical models, THC has demonstrated proconvulsive properties. Most epilepsy studies have focused on CBD and its analog cannabidivarin. Unlike Δ9-THC, CBD has very low affinity for CB1 and CB2 receptors (which would explain its low psychotropic activity), for which reason it has been suggested that CBD's antiepileptic mechanism is independent of the endocannabinoid system [17]. At present, the exact mechanism of action in epilepsy is unknown, however, some hypotheses have been raised: it modulates the ENT transporter, the GPR55 receptor and the TRPM8 channel, which are involved in neuronal hyperexcitability phenomena.

Cannabinoids with an antioxidant profile, that is, Δ9-THC and CBD, protect strial neurons against toxicity caused by the 3-nitropropionic acid (3NP) inhibitor mitochondrial complex II that produces oxidative injury [18]. They alleviate hyperkinetic symptoms, given their inhibitory effects on movement and, in particular, are being studied as disease modifying agents due to their anti-inflammatory, neuroprotective and neuroregenerative properties [19].

It also modulates the activation of the serotonin receptor 5HT1a, some glycine receptors and the TRPA1 channel, which help regulate intracellular calcium concentrations. Additionally, CBD is a powerful inhibitor of certain liver enzymes (CYP3A4, CYP2C9 and CYP2C19), therefore it inhibits the metabolism of some antiepileptic drugs that use the same enzymatic system, enhancing their antiepileptic properties; this is the case of clobazam, topiramate, zonisamide and eslicarbazepine [20]. CBD has a very low oral bioavailability (less than 10%), which is explained, in part, by a large first-pass metabolism in the intestine and liver. The elimination

half-life ranges between 18-32h, allowing administration once or twice a day. Some studies have suggested that the associative effects of all plant components are more effective than isolated chemicals (CBD and Δ9-THC). This phenomenon is known as the entourage effect. This shows that the clinical effects of cannabis are secondary to complex interactions between the different cannabinoids and are not the consequence of the action of an isolated chemical compound. To support this hypothesis, some studies have shown that CBD enhances some beneficial properties of Δ9-THC and reduces its psychoactivity, improving tolerance. Apparently, CBD has the ability to counteract some functional consequences of the activation of CB1 receptors in the central nervous system. This could be the explanation for why cannabis users with a high CBD:THC ratio experience few psychotropic effects compared to those who use cannabis with a low CBD:THC ratio [21].

Preclinical Research in different cancers

In recent years, experiments have been carried out in tumor cell cultures and in animal models of cancer that suggest that the combination of cannabinoids and standard antitumor therapies might work better than either approach alone. A high percentage of cancer patients receive chemotherapy. This treatment targets the cells of the organism that are in proliferation and seeks to block their division and cause their death. This can be achieved through several general strategies, the most common of which are to interfere with the duplication process of the cells' genetic material and to block the reorganization of the cytoskeleton (internal scaffolding of cells that shapes, allows their movement and governs the physical separation of cells. two daughter cells in the processes of cell division). The tools to block the duplication of DNA in tumor cells are very varied, and include compounds that incorporate alkyl groups (such as temozolomide), bridges between DNA chains (such as cisplatin), analogs of its structural components (such as 5-fluorouracil; 5-FU) or inhibitors of the machinery that maintains DNA topology during the process of cell division (such as irinotecan). Preclinical studies show that cannabinoids not only do not hinder the antitumor action of representatives of many of these families but also enhance it. For example, 5-FU reduced the viability of colorectal cancer cells in culture much more effectively when combined with the cannabinoid agonist HU-210 and include compounds that incorporate alkyl groups (such as temozolomide), bridges between DNA strands (such as cisplatin), analogs of their structural components (such as 5-fluorouracil; 5-FU) or inhibitors of the machinery that maintains the topology of DNA during the process of cell division (such as irinotecan) [22]. Preclinical studies show that cannabinoids not only do not hinder the antitumor action of representatives of many of these families but also enhance it. For example, 5-FU reduced the viability of colorectal cancer cells in culture much more effectively when combined with the cannabinoid agonist HU-210 and include compounds that incorporate alkyl groups (such as temozolomide), bridges between DNA strands (such as cisplatin), analogs of their structural components (such as 5-fluorouracil; 5-FU) or inhibitors of the machinery that maintains the topology of DNA during the process of cell division (such as irinotecan). Preclinical studies show that cannabinoids not only do not hinder the antitumor action of representatives of many of these families but also enhance it. For example, 5-FU reduced the viability of colorectal cancer cells in culture much more effectively when combined with the cannabinoid agonist HU-210 5-FU) or inhibitors of the machinery that maintains DNA topology during the process of cell division (such as irinotecan). Preclinical studies show that cannabinoids not only do not hinder the antitumor action of representatives of many of these families but also enhance it. For example, 5-FU reduced the viability of colorectal cancer cells in culture much more effectively when combined with the cannabinoid agonist HU-210 5-FU) or inhibitors of the machinery that maintains DNA topology during the process of cell division (such as irinotecan). Preclinical studies show that cannabinoids not only do not hinder the antitumor action of representatives of many of these families but also enhance it. For example, 5-FU reduced the viability of colorectal cancer cells in culture much more effectively when combined with the cannabinoid agonist HU-210. Along the same lines, Guillermo Velasco's group (Complutense University) has described that the combination of temozolomide and Δ9-tetrahydrocannabinol (THC) in an animal model of glioblastoma produces a greater inhibition of tumor growth than either of the two treatments separately. With respect to drugs that target the cytoskeleton of dividing cells, paclitaxel has been shown to have synergistic effects when combined with the endocannabinoid anandamide: in a gastric cancer cell model, the combination of both compounds produced more cell death due to apoptosis than either of the two compounds separately [23,24].

In addition to chemotherapy, many cancer patients receive radiotherapy treatment, which consists of exposing tumor cells to high-energy radiation to cause alterations in them that slow down

their division and induce their death. As in the case of chemotherapy, there is preclinical evidence suggesting that cannabinoids could sensitize tumors to this type of treatment. Thus, Scott et al. Demonstrated that the combination of submaximal doses (that is, they exerted very discrete antitumor effects by themselves) of both THC + cannabidiol (CBD) and radiation, produced a drastic reduction in the growth of glioblastomas generated in mice [14,25].

Antitumor therapy

In recent years, studies have brought to light preclinical evidence of the ability of cannabinoids to reduce tumor growth in animal models, and clinical trials have been designed to study this activity in patients with glioblastoma. The data in animal models show promising results, but clinical research is needed to determine if this practice can be successfully applied to human therapy and which type of cancer and patient would respond satisfactorily to this treatment [14].

It has been observed that the receptors and ligands of the endocannabinoid system are overexpressed in tumor tissues, and it is postulated that in these tissues they exert antitumor properties through four mechanisms. Antitumor modes of action include: induction of apoptosis in tumor cells; selectivity for tumor cells; inhibition of cell proliferation; and inhibition of angiogenesis, invasion, and metastasis [26].

The greatest advances in the investigation of antitumor therapy with cannabinoids have been carried out in the glioblastoma model, whose current treatment includes diagnosis, surgery, radiotherapy and pharmacological treatment with temozolomide. From 2003 to 2006, a pilot clinical trial with nine patients was developed to demonstrate a favorable safety profile of THC, observing that the treatment with THC was safe and that the evidence obtained in preclinical could be taken to the clinic to try to demonstrate the mechanisms that had been described in animal models. More recently, from 2014 to 2016, a single clinical trial has been conducted with the specific objective of analyzing the combined effect of cannabinoids and an antitumor drug. In this trial, carried out in hospitals in the United Kingdom and Germany, in patients with recurrent glioblastoma, the safety and efficacy of the combination of temozolomide and Sativex, a cannabinoid drug that contains approximately the same amount of THC and CBD, has been analyzed (NCT01812616). Although the results of this trial have not yet been published, the press release issued by the sponsoring company (GW Pharmaceuticals) appears to indicate that there have been no negative drug interactions.

Although this is the only clinical trial designed specifically to analyze the safety of combined treatments, it is important to note that many trials have been carried out with cannabinoid drugs in an oncology population that followed their conventional antitumor treatments. For example, and only with Sativex, seven clinical trials have already been conducted in cancer patients to analyze its effect on cancer pain. In none have negative drug interactions been reported. Neither have negative effects associated with the combination of drugs been detected in other trials carried out to analyze the analgesic effect of cannabinoid drugs in cases of neuropathic pain caused by chemotherapy itself [27].

The company GW-Pharmaceuticals has carried out a placebo-controlled phase II clinical trial where patients, who after receiving conventional treatment have suffered a relapse, are administered temozolomide plus a THC:CBD preparation in 1: 1 proportions. The company has already announced still inconclusive but positive results of an increase in the survival rate of patients [28].

Recent findings show that TMZ + THC:CBD combinations containing a higher proportion of CBD (but not TMZ + CBD alone) produce an antitumor effect similar to the administration of TMZ together with THC and CBD in a 1: 1 ratio. In xenografts generated with glioma cell lines. Furthermore, was also found that the administration of TMZ + THC:CBD in a 1: 1 ratio reduced the growth of GIC(glioma initiator cells)-generated orthotopic xenografts derived from GBM patients and improved the survival of animals bearing these intracranial xenografts. The antitumor effect observed in GIC-derived xenografts was stronger when TMZ was administered in conjunction with cannabinoid combinations containing a higher proportion of CBD [29,30].

Conclusion

Taking into account all the above, the truth is that in the absence of results from clinical trials (which will still take years to provide conclusive data) at this time there is not enough scientific evidence to be able to conclusively affirm that cannabinoid treatment can contribute improve current therapies given to patients with brain tumors or other types of tumors. This means that the administration of cannabinoid drugs or medicinal cannabis as part of the standard treatment for the treatment of these diseases is not authorized (nor therefore subsidized).

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