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The role of cannabinoids in prostate cancer: Basic science perspective and potential clinical applications

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Abstract

Prostate cancer is a global public health problem, and it is the most common cancer in American men and the second cause for cancer-related death. Experimental evidence shows that prostate tissue possesses cannabinoid receptors and their stimulation results in anti-androgenic effects. To review currently relevant findings related to effects of cannabinoid receptors in prostate cancer. PubMed search utilizing the terms "cannabis," "cannabinoids," "prostate cancer," and "cancer pain management," giving preference to most recent publications was done. Articles identified were screened for their relevance to the field of prostate cancer and interest to both urologist and pain specialists. Prostate cancer cells possess increased expression of both cannabinoid 1 and 2 receptors, and stimulation of these results in decrease in cell viability, increased apoptosis, and decreased androgen receptor expression and prostate-specific antigen excretion. It would be of interest to conduct clinical studies utilizing cannabinoids for patients with metastatic prostate cancer, taking advantage not only of its beneficial effects on prostate cancer but also of their analgesic properties for bone metastatic cancer pain.

Keywords: Androgen antagonists, cannabis, cannabinoids, investigational therapies, prostatic neoplasms

INTRODUCTION

Prostate cancer is an established public health concern in modern society and has been for decades. It is the most common cancer in men (asides from non-melanoma skin cancer) and the second most common cause of cancer death in the United States.[1] Even with widespread screening with prostate-specific antigen (PSA), still 5% of cases present with metastatic lesions at the time of diagnosis.[2] Because of all this, there is a fundamental necessity to search for and find new and novel treatments to this common pathology. Cannabis and cannabinoids have often been an issue of much polemics in the realm of science, but since the discovery of cannabinoid receptors in rat brain in the late 1980s,[3] there has been a growing interest in the research of these compounds and our knowledge continues to expand. There has been experimental evidence that cannabinoids possess anti-androgenic proprieties; the purpose of this review is to describe in detail the effects, characteristics, and possible role of cannabis and cannabinoids in the subject of prostate cancer.

MATERIALS AND METHODS

A PubMed search was conducted for manuscripts published regardless of publication date, which contained the terms “cannabis,” “cannabinoids,” “prostate cancer,” and “cancer pain management,” giving preference to most recent publications. Articles identified were screened for their relevance to the field of prostate cancer and likely interest to both urologist and pain specialists. This review article focuses on the effects of cannabinoids in the realm of prostate cancer pathophysiology and their potential uses.

Overview: Prostate cancer Prostate cancer is the most common cancer in American men except for non-melanoma skin cancer. In the United States, an estimated 217,730 cases will be diagnosed in 2010 and 32,050 deaths will occur.[1] Its frequency has increased in part due to the widespread availability of serum PSA testing. Its incidence peaked in 1992, declined between 1992 and 1995, and has been rising about 1% annually since then[1,4] until 2000-2006, since then incidence rates have declined by 2.4% per year, which may reflect recent stabilization of PSA testing.[5–7] Widespread PSA use has led to an increasing proportion of prostate cancer cases that are localized at diagnosis, with fewer patients presenting with metastatic disease. As an example, between 1984 and 1991, 30–40% of men presented with advanced disease,[8] and currently only 5% have distant metastases at the time of diagnosis.[2] Prostate cancer remains the second most common cause of cancer death in American men.[1]

Despite the fact that a higher percentage of men have localized disease at presentation, metastatic prostate cancer remains an important clinical problem, both in terms of the number of affected men and its impact on their quality of life. Hematogenous spread of prostate cancer cells is a common event. For these malignant cells, tumor growth preferentially occurs in bones of the axial skeleton. The most common site of metastasis is bone and frequently is symptomatic, causing pain, debility, and functional impairment.[9] The presence of pain in men with advanced prostate cancer is an immediate indication for aggressive management with analgesics, while adequate treatments that address directly the cause of the pain are pursued.[10]

Numerous treatment options have been established to treat bone metastatic prostate cancer; some focus on treating the underlying pathophysiology, while others focus on pain management and palliative care. Examples of the former are androgen deprivation therapy (ADT), being the initial approach in most cases, it alleviates pain from bone metastases to 80–90%.[9] Second-line hormonal therapy with systemic chemotherapy with docetaxel and mitoxantrone,[11,12] may be beneficial when the initial ADT regimen is no longer effective. More local modalities also considered in today's medical world are focal external beam radiation therapy, an excellent treatment choice for men with castrate-resistant prostate cancer and bone pain that is limited to one or a few sites, bone-targeted radioisotopes 89-strontium (89Sr) and 153-samarium (153Sm) for multiple blastic bone lesions, and radiofrequency ablation.[9]

Role of cannabinoids in male physiology Cannabis is a bushy plant with palmate leaves and clusters of small green flowers, and it grows wild in regions of tropical weather and can attain up to 3 m height. The genus Cannabis is complemented by sativa which translates to useful. Cannabis has indeed been used throughout history for a variety of purposes, including the production of fiber for paper and textile manufacture. However, its current popularity lies in its use as a recreational drug with psychoactive properties. The plant contains many chemical compounds that have different pharmacological properties, varying in quantity and quality depending on the strain, culture, and storage conditions.[13]

In 1964, Mechoulam and colleagues[14] found that delta-9-tetrahydrocannabinol (THC) was the major psychoactive ingredient of cannabis. However, the endocannabinoid signaling system has only been the focus of medical research and considered a potential therapeutic target in recent times.[15–17] During the late 1980s Howlett and colleagues[3] identified and characterized a receptor in rat brain that met criteria for a high-affinity, stereoselective, pharmacologically distinct cannabinoid receptor, by means of radiolabelled agonist ligand binding and functional assays for G-protein coupled receptors.

Two different cannabinoid receptors have been described from mammalian tissues: the “central”

Cannabinoid 1 (CB1) receptor[18] and the "peripheral" Cannabinoid 2 (CB2) receptor.[19]

In the United States, cannabis has been illegal since 1937,[15] and currently 14 states (Alaska, California, Colorado, Hawaii, Maine, Michigan, Montana, Nevada, New Jersey, New Mexico, Oregon, Rhode Island, Vermont, and Washington) and DC have enacted laws that legalize medical marijuana,[20] requiring it to be prescribed by physicians and being especially used to relieve AIDS patients treatment side effects. The frequently held view of cannabis and its related products as drugs of abuse have slowed progress in the development of studies designed to take advantage of the properties of cannabinoid derivatives for therapeutic purposes.[13]

The antagonizing effect of cannabinoids in the male reproductive system and physiology can be dated to 1974 where experimental models in male rats showed depression of spermatogenesis[21] and decrease in circulating testosterone levels.[22] Chakravarty and colleagues[23,24] in 1980-1981 demonstrated how administration of cannabis reduced levels of fructose and citric acid, and decreased glucuronidase, glycosidase, and acid phosphatase levels in accessory reproductive organs of male rats, most of these which are regulated by circulating levels of testosterone, suggesting at the time a possible anti-androgenic effect of cannabis.

Current basic science research In recent years, cannabinoids and their derivatives have drawn renewed attention due to the discovery of diverse pharmacologic activities such as cell growth inhibition, anti-inflammatory effects, and tumor regression.[25–30] Focusing on prostate cancer, in 2005, Sarfaraz and colleagues[30] showed that expression of both CB1 and CB2 receptors was significantly higher in cultured prostate cancer cells LNCaP, DUI45, PC3, CWR22Rr1, and CAHPV-10 when compared with normal prostate cells PZ-HPV-7 and PrEC. Data also show that treatment of LNCaP prostate cancer cells with cannabinoid CB1/CB2 agonist WIN-55,212-2 results in a significant dose- and time-dependent decrease in cell viability and increased apoptosis of the former at 24 and 48 hours, with no significant change in apoptosis of the normal prostate epithelial cells at similar doses. When the same cells were pretreated with cannabinoid receptor antagonists SR141716 (CB1 antagonist) or SR144528 (CB2 antagonist), the coadministration of WIN-55,212-2 had no effect on cell viability, exhibiting a significant protective effect. These data suggest that both CB1 and CB2 receptors may be involved in WIN-55,212-2-mediated growth inhibition and apoptosis.[30]

Androgens are involved in the maintenance and progression of prostate cancer, where the androgen receptor is assumed to be the essential mediator for androgen action.[31,32] Sarfaraz' study also showed that stimulation of cannabinoid receptors resulted in a marked decrease in androgen receptor protein expression and a dose-dependent decrease in PSA expression and secreted PSA (secreted levels of PSA decreased by 30%, 53%, and 62 % at 5.0, 7.5, and 10 Amol/L, respectively) at 24 hours.[30] PSA is considered as the most sensitive biomarker and screening tool for prostate cancer to date; its regulation is androgen-dependent.[33]

On a future study, Sarfaraz and colleagues[34] revealed the molecular bases for increased apoptosis and cell inhibition in prostate cancer cells treated with cannabinoid agonists, showing that treatment with WIN-55,212-2 resulted in arrest of the cells in the G0/G1 phase of the cell cycle; induction of p53 and p27/KIP1 genes; down-regulation of cyclins D1, D2, E; decrease in the expression of cdk-2, -4, and -6; and decrease in the protein expression of DP1and DP2. Curiously enough it was determined that high cannabinoid CB1 receptor immunoreactivity is associated with greater disease severity and poorer outcome in prostate cancer patients.[35] In this study, 42% of the high CB1 receptor immunoreactivity group on prostate biopsy presented with Gleason scores of 8–10 when compared with 12% in the low CB1 receptor immunoreactivity. The incidence of metastases at diagnosis was also higher in the high CB1 receptor immunoreactivity (17%) than in the low group (5%). Patients with high CB1 receptor immunoreactivity

showed a significantly worse survival rate than those with low CB1 receptor immunoreactivity (hazard ratio 2.51, with 95% confidence limits of 1.43–4.43; $P < 0.05$). A possible explanation for these results that is in synch with the cell line data is that the expression of CB1 receptors is regulated by the local endocannabinoid release. The author's conclusion in this scenario was that a low endocannabinoid tone would allow for an increased rate of proliferation, resulting in a compensatory increase in surface expression of CB1 receptors.[35]

Cannabinoids in cancer pain management Cannabinoid CB1 receptors are found mainly in the central nervous system and, in less abundance, in certain peripheral tissues.[36] At the peripheral level, they are localized in the adrenal gland, adipose tissue, heart, liver, lung, prostate, uterus, ovary, testis, bone marrow, thymus, tonsils, and presynaptic nerve terminals.[37–42] More significantly for the purposes of the present review, they are found at central and peripheral levels of the pain pathways.[39–47] The distribution of cannabinoid receptors provides an anatomical explanation for the analgesic effects of the cannabinoids. Activation of presynaptic CB1 receptors in different brain regions or on primary afferents inhibits the release of neurotransmitters by decreasing calcium conductance and by increasing the conductance of potassium.[42] Neurophysiological studies by Walker's laboratory first documented that cannabinoids suppress nociceptive processing.[48–50] Cannabinoids, administered systemically, suppress activity of nociceptive neurons in the spinal dorsal horn[48] and ventralposterior lateral nucleus of the thalamus, without altering the activity of purely non-nociceptive neurons.[49] Stimulation-produced analgesia was blocked by the CB1 antagonist SR141716A, demonstrating mediation by the CB1 receptor.[51]

Delta-9-THC is the substance with the greatest psychoactive potency of the natural cannabinoids and exhibits the greatest analgesic activity.[52] Cannabidiol (CBD), another major constituent of the Cannabis sativa plant, has the same therapeutic effects of THC (analgesic, anti-inflammatory, and others), but with a different pharmacologic profile. Studies with CBD derivatives developed to inhibit peripheral pain responses and inflammation after binding to cannabinoid receptors have been described. Interestingly, some of these CBD derivatives did not have central nervous system effects, but maintained their antinociceptive and anti-inflammatory properties. This means that centrally inactive synthetic CBD analogues may be candidates for the development of analgesic and anti-inflammatory drugs for peripheral conditions[53] without major central nervous system alterations of the sensorium.

In animal models of cancer bone pain, synthetic cannabinoids reduced hyperalgesia by a CB1 receptor-mediated effect and possibly at the peripheral CB2 receptor. In some models, cannabinoids were superiorly effective in cancer pain when compared with other pain types.[54–58]

Clinical trials have shown that nonselective cannabinoid receptor agonists are relatively safe and therapeutically efficacious, however, inducing also psychotropic side effects.[59]

Cannabinoid efficacy has also been studied clinically in cancer pain. Initial studies quantified the modest efficacy of oral 20 mg D9-THC equivalent to 120 mg codeine with some sedation, dizziness, and confusion.[54,60,61] Recently in an observational study of patients with advanced cancer pain, nabilone reduced pain scores, total opioid requirements, and nausea. Nabilone did not significantly increase adverse effects compared with the control group, and this fact could be attributed to the concurrent decrease in opioid dose.[62]

Uncontrolled pain can cause unnecessary suffering, decreased ability to cope with illness, interference with daily activities and extended hospital admissions, and decreasing overall quality of life.[63,64] The usual approach to cancer pain management differs from physician to physician, but a well-known guideline is described in the World Health Organization's analgesic ladder:[65,66]

Step 1 of the ladder is for patients with mild to moderate cancer-related pain. These should first be treated

with acetaminophen or a nonsteroidal antiinflammatory agent (NSAID), possibly combined with an adjuvant drug that provides additional analgesia (i.e., an analgesic antidepressant drug for neuropathic pain), treats a side effect, or manages a coexisting symptom.

Step 2 describes patients with moderate or severe pain, including those who do not achieve adequate relief after a trial of an NSAID alone; these should be treated with an opioid.

The analgesic ladder promoted the doctrine of using an opioid of inferior analgesic properties (i.e., codeine as the prototype) to treat pain of moderate intensity on step 2 and strong opiates as morphine or hydromorphone for severe pain on step 3.

On both steps 2 and 3, combination therapy that includes an NSAID or other drugs to enhance analgesia or treat side effects is advocated.

The combination of two antinociceptive drugs acting through different specific receptor systems provides major benefits. When synergistic substances are given in combination, the required dose of each agent can be reduced to less than would be explained by mere addition of individual effects. The clinical benefit of this property is fundamental in analgesic treatments because effective pain relief can be achieved with minor, fewer, or no side effects.[13]

Chronic pain is a difficult subject to approach both for the patient and the treating physician and, not uncommonly, leads to chronic opiate consumption and dependence.[67] Physician and the patients both are left with less and less options, and eventually to resort to alternative modes of therapy. Cannabis has been documented to be one of such measures.[68]

As with any therapeutic modality, adverse effects must be taken into account. A number of patients will suffer from these, although most of them will be present within the first days of treatment and attenuate as they adjust to the drug. Some effects described with cannabis use are short-term unsteadiness, dizziness, difficulty concentrating, drowsiness, dryness of the mouth, and/or headache. Chronic cannabis use does not produce serious cognitive disorders, as occurs with other substances such as alcohol, but it can aggravate preexisting mental disease. Therefore, treatment with cannabinoid receptor agonist with central actions may be contraindicated, in individuals predisposed to or with current psychiatric disorders. No human deaths associated to cannabis use have been reported.[13]

DISCUSSION

Prostate cancer is a grave public health problem worldwide. Despite the fact that most cases currently present with localized disease at the time of diagnosis, about 5% of men still present with metastatic disease.[2] The most common site of spread is bone, and these lesions are frequently symptomatic, causing pain, debility, and functional impairment.[9] Many of these men do not have curative treatment options, and this remains a crucial clinical problem, both in terms of the number of men affected and its impact on their quality of life. For these reasons, it is fundamental to invest time and intellectual resources into finding new and novel targets for the treatment of prostate cancer.

It seems that the studies of Sarfaraz and colleagues lead to the direction that cannabinoids should be considered as agents for the management of prostate cancer, pending support from *in vivo* experiments. This would not only make sense from an anti-androgenic point of view but also for men with bone metastatic prostate cancer, perhaps from a pain management or palliative point of view. Among the patients suffering with chronic pain and receiving opioids, one in five abuse prescription controlled substances,[69,70] and it is not difficult to see that opioid dependence and abuse is becoming a public health problem. Different methods of managing pain should be addressed to avoid these scenarios.

The presence of pain in men with advanced prostate cancer is an immediate indication for aggressive management with analgesics, while adequate treatments that address directly the cause of the pain are pursued.[10] Cannabinoids possess attributes that have impact in both cancer pain and prostate cancer pathophysiology. These compounds harbor analgesic properties that aid bone cancer pain, reduce opioid consumption, side effects, and dependence, as well as exhibiting anti-androgenic effects on experimental prostate cancer cells.

CONCLUSION

Cannabis sativa and its main active component delta-9-THC have long been used for numerous purposes throughout history including medicinal, textile, and recreational. Since its legal banning in the United States in 1937, it has become an issue of taboo and controversy, frowned upon for its recreational uses and psychotropic effects. Nonetheless, the endocannabinoid signaling system has recently been the focus of medical research and considered a potential therapeutic target[15–17] since the late 1980s when Howlett and colleagues[3] identified and characterized the distinct cannabinoid receptor in rat brain. The antagonizing effect of cannabinoids in the male reproductive system and physiology can be dated to 1974 where experimental models in male rats showed depression of spermatogenesis[21] and decrease in circulating testosterone levels.[22] In 2005, Sarfaraz and colleagues[30] showed increased expression of both CB1 and CB2 receptors in cultured prostate cancer cells when compared with normal prostate cells, treatment of prostate cancer cells with cannabinoid CB1/CB2 agonist WIN-55,212-2 results in a dose and time dependent decrease in cell viability ,and increased apoptosis along with decrease in androgen receptor protein expression, PSA expression, and secreted PSA, suggesting that cannabinoids should be considered as agents for the management of prostate cancer. If the hypothesis is supported by *in vivo* experiments. It is our conclusion that it would be of interest to conduct clinical trials involving medicinal cannabis or other cannabinoid agonists, comparing clinical markers such as PSA with controls, especially in men with bone metastatic prostate cancer, whom would not only benefit from the possible anti-androgenic effects of cannabinoids but also from analgesia of bone pain, improving quality of life, while reducing narcotic consumption and preventing opioid dependence.

Footnotes

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Conflict of Interest: None declared.

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