Off the Wall!

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Cannabis for Inflammatory Bowel Disease

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Cannabidiol · Cannabis · Inflammatory bowel disease · Crohn's disease · Δ9-Tetrahydrocannabinol · Ulcerative colitis

Abstract
The marijuana plant *Cannabis sativa* has been used for centuries as a treatment for a variety of ailments. It contains over 60 different cannabinoid compounds. Studies have revealed that the endocannabinoid system is involved in almost all major immune events. Cannabinoids may, therefore, be beneficial in inflammatory disorders. In murine colitis, cannabinoids decrease histologic and microscopic inflammation. In humans, cannabis has been used to treat a plethora of gastrointestinal problems, including anorexia, emesis, abdominal pain, diarrhea, and diabetic gastroparesis. Despite anecdotal reports on medical cannabis in inflammatory bowel disease (IBD), there are few controlled studies. In an observational study in 30 patients with Crohn's disease (CD), we found that medical cannabis was associated with improvement in disease activity and reduction in the use of other medications. In a more recent placebo-controlled study in 21 chronic CD patients, we showed a decrease in the CD activity index >100 in 10 of 11 subjects on cannabis compared to 4 of 10 on placebo. Complete remission was achieved in 5 of 11 subjects in the cannabis group and 1 of 10 in the placebo group. Yet, in an additional study, low-dose cannabidiol did not have an effect on CD activity. In summary, evidence is gathering that manipulating the endocannabinoid system can have beneficial effects in IBD, but further research is required to declare cannabinoids a medicine. We need to establish the specific cannabinoids, as well as appropriate medical conditions, optimal dose, and mode of administration, to maximize the beneficial effects while avoiding any potential harmful effects of cannabinoid use.

Introduction

The plant *Cannabis sativa* contains at least 70 different cannabinoids. Of these, the most important psychoactive compound is Δ9-tetrahydrocannabinol (THC). Other important compounds include cannabidiol (CBD), cannabigerol, and cannabichromene. Cannabinol is an oxidation product of THC and an indication that the herb has deteriorated. Olivetol is the biosynthetic precursor.

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These phytocannabinoids exert their effects through binding to specific membrane receptors and manipulating the endocannabinoid system.

The Endocannabinoid System

The endocannabinoid system is an important regulatory lipid signaling system found in all vertebrates and throughout the human body [1]. It consists of cannabinoid receptors, their endogenous ligands, collectively known as endocannabinoids, and the enzymes that synthesize and degrade the ligands.

Two major cannabinoid receptors are currently known, CB1 and CB2. Both are G protein-coupled receptors. CB1 is expressed mainly by neurons in the brain, spinal cord, peripheral nervous system, and enteric nervous system. To a lesser extent, it is also expressed in other organs and tissues including the spleen, heart, lung, intestine, kidney, reproductive organs, skeletal muscle, and skin. CB2 receptors appear to be expressed mainly by cells of the immune system. It has recently been shown that endocannabinoids are also agonists for TRPV1 (transient receptor potential vanilloid subtype 1; also called VR1) receptor, the receptor for the plant compound capsaicin and also for the peroxisome proliferator-activated receptor family [1]. Moreover, GPR55, an orphan G-protein coupled receptor, was suggested to be involved in non-CB1-, non-CB2-mediated actions of cannabinoids, but additional characterization is still required [1].

The endogenous ligands for the cannabinoid receptors include the endocannabinoids anandamide (arachidonoyl ethanolamide) and 2-arachidonoyl glycerol (2-AG). Endocannabinoids are derivatives of arachidonic acid conjugated with ethanolamine or glycerol. They have been found in the brain and plasma as well as in peripheral tissues. Anandamide is a partial agonist of cannabinoid receptors and binds with slightly higher affinity to CB1 than to CB2, while 2-AG appears to bind equally well to both CB receptors with a greater potency and efficacy than anandamide [2].

The in vivo biosynthesis of anandamide is believed to occur through the enzymatic hydrolysis catalyzed by phospholipase D of a membrane lipid precursor, N-arachidonoyl phosphatidylethanolamide [3]. The endocannabinoid 2-AG is generated from diacylglycerol by its lipase, which is selective for the sn-1 position [4]. The endocannabinoids are degraded by the enzymes fatty acid amide hydrolase and monoacylglycerol lipase [1].

Actions of Endocannabinoids

The endocannabinoid system modulates several physiological processes, mainly in the brain, including effects on nociception, memory processes, plasticity, and cell proliferation [5]. Endocannabinoids also play a peripheral modulatory role affecting the immune and cardiovascular systems, as well as reproductive endocrine processes and control of energy metabolism [6]. Anandamide is able to produce analgesia, control motor activity, reduce emesis, stimulate appetite, and induce hypothermia. It also presents antiproliferative effects [7]. 2-AG acts as a messenger molecule in various biological systems, such as the endocrine and immune systems. However, the exact physiological roles of 2-AG remain poorly understood [8]. In the gastrointestinal (GI) tract, activation of prejunctional CB1 receptors reduces excitatory enteric transmission (mainly cholinergic), thereby leading to inhibition of motility [9]. CB1 activation has an inhibitory effect on gastric transit, and also a well-known anti-emetic effect, including inhibition of the apomorphine-induced emetic response [10]. CB2 activation efficaciously counteracts alterations in intestinal motility during inflammatory conditions, but not in healthy animals. It also participates in the control of gut inflammation, as evidenced in mouse models of colitis induced by trinitrobenzene sulfonic acid [11] and in CB2–/– mice [12].

Phytocannabinoid Effects

Much of the pharmacodynamic information on phytocannabinoids refers to the effects of the major constituent of cannabis, Δ9-THC. It acts as a partial agonist of both cannabinoid receptors. However, it also activates non-CB receptors and other targets [13]. It is responsible for the psychoactive effects of cannabis mainly through its actions on the CB1 receptor [14].

CBD is the other important natural cannabinoid, and in fact one of the few which have been investigated pharmacologically. It does not appear to bind to either CB1 or CB2 receptors at physiologically meaningful concentrations, but it affects the activity of a significant number of other targets, including ion channels, receptors and enzymes [15].

Pharmacological evidence in animal models suggests that not all the observed therapeutic effects of the cannabis herb can be ascribed to the THC content, or indeed to any single cannabinoid. For example, CBD, which is not psychotropic in itself, has been demonstrated to be anx-

iolytic in animals and humans, and to reduce the anxiety reaction occasionally induced by THC [16]. CBD elevates THC levels and those of other drugs in the mouse brain [17]. Therefore, it is possible that a standardized extract of the herb, containing predetermined amounts of THC and CBD, and possibly some of the other components, may be more beneficial in practice than any single compound.

Dose and Route of Administration

The bioavailability of cannabis preparations has not been well investigated. The quickest and most reproducible method of obtaining an effect of cannabis is by smoking. Where subjective assessment of the effect is needed, smoking enables some form of self-titration of dose. Smoking carries its own dangers, although for some these may be tolerable if relief of severe chronic pain is achieved. The respiratory side effects of cannabis have not been well studied, but there is strong evidence that cannabis causes bronchial inflammation and respiratory symptoms, and affects lung function [18]. During smoking, the acids are decarboxylated to the active free cannabinoids. This may explain why giving cannabis orally is less effective than smoking it. Recreational cannabis users are well aware of this fact, which has also been demonstrated clinically [19].

The safety of cannabis and the cannabinoids is surprisingly good, but for therapeutic use most patients prefer to remain alert, requiring a fairly narrow dosage range that will reduce pain and nociception without adverse effects such as drowsiness and lack of concentration. A study from the Netherlands tracking data obtained from the Dutch medical cannabis program during the years 2003–2010 reported that in a population of over 5,000 patients using cannabis for medical purposes, the average daily dose of dried cannabis (various potencies) was 0.68 g per day (range: 0.65–0.82 g per day) [20].

Metabolism

THC enters the bloodstream rapidly after smoking. Because of its lipophilicity, it is absorbed into fat tissue, where it may be detected for over 4 weeks. It is gradually released back into the blood stream. THC is fairly quickly converted to 11-hydroxy-THC, a metabolite which is equipotent with THC itself, to 11-nor-9-carboxy-Δ9-THC, which is inactive, and to other cannabinoids, primarily by cytochrome P_{450} enzymes [21]. The relatively slow elimination from the body has implications regarding safety for cognitive tasks, especially relating to driving and operating machinery. This is of major importance if therapeutic use of cannabinoids is to be considered [22].

Clinical Effects of Cannabinoids

Most of the available information regarding the acute effects of smoking cannabis comes from studies conducted on recreational users, with much less information available from patients using cannabis for medical purposes. Since recreational users are more likely to combine cannabis use with alcohol and other drugs, the information should be interpreted with caution. The acute effects of smoking or eating cannabis include euphoria, relaxation, time distortion, intensification of ordinary sensory experiences, and loss of inhibitions. These effects are attributed mostly to THC. Other effects include cardiovascular, ocular, bronchopulmonary, psychological, and psychomotor effects.

Results from preclinical studies suggest that CBD has anti-inflammatory, analgesic, anti-nausea, anti-emetic, anti-psychotic, anti-ischemic, anxiolytic, and anti-epileptic effects [23]. It has a modulating effect on brain THC levels, but also intrinsic activity by itself. Although not psychoactive, it has a potent analgesic and anti-inflammatory effect mediated by dual cyclooxygenase and lipoxygenase inhibition. This anti-inflammatory effect is several hundred times more potent than that of aspirin (acetylsalicylic acid), when measured in standard animal tests and isolated cell assays [24]. However, after oral administration, it appears to act mainly as a lipoxygenase inhibitor. CBD, like THC, also stimulates the release of prostaglandin E_2 from synovial cells and, like THC, inhibits leukotriene B_4 synthesis in human polymorphonuclear cells in vitro [5, 24].

Adverse Effects and Interactions

Cannabis itself has a remarkably good safety profile, with a therapeutic index estimated at 1:40,000. Adverse reactions to cannabis include panic or anxiety attacks, which are worse in the elderly and in women, and less likely in children. They are mainly due to THC and are lessened by the presence of CBD [25].

Psychiatric disorders, if already present, may be exacerbated but are rarely induced de novo. The amotivational syndrome (a psychological condition associated with

Table 1. Cannabinoids in various murine models of experimental colitis

Ref.	Model	Treatment	Results
33	Cholera toxin-induced diarrhea in mice	Anandamide	Inhibition of fluid accumulation in the small intestine
34	DNBS mouse colitis	CB1-knockout mice	More severe and extensive colitis
34	DNBS mouse colitis	Pharmacological blockade of the CB1 receptor	More severe and extensive colitis
34	DNBS mouse colitis	CB receptor agonist HU-210	Ameliorated colitis
35	TNBS colitis	Genetic deletion of either CB1, CB2 or both CB receptors	More severe and extensive colitis
36	DNBS mouse colitis	Injection of cannabidiol (5–10 mg/kg i.p.)	Reduced colonic inflammation and weight loss
37	TNBS mouse colitis	Cannabidiol (10 mg/kg i.p.)	Significant improvement in colitis
37	TNBS rat colitis	Intrarectal cannabidiol (20 mg/kg)	Significant improvement in colitis
37	TNBS rat colitis	Cannabidiol (20 mg/kg p.o.)	No improvement in colitis
38	TNBS rat colitis	CBD, THC, or both THC and CBD vs. sulfasalazine	Decrease in macroscopic colitis and myeloperoxidase activity
39	Oil of mustard and DSS-induced colitis	ACEA (a CB1 receptor agonist) and JWH-133 (a CB2 receptor agonist)	Significant improvement in colitis
40	TNBS colitis	Inhibition of the 2-AG-degrading enzyme MAGL	Reduction in both microscopic and histological inflammation
40	TNBS colitis and MAGL inhibitor	CB1 or CB2 receptor antagonists	Effect of MAGL inhibition abolished

DNBS = Dinitrobenzene sulfonic acid; TNBS = trinitrobenzene sulfonic acid; DSS = dextran sulfate sodium; MAGL = monoacylglycerol lipase.

diminished inspiration to participate in social situations and activities) was described among long-term cannabis users [26]. The problem of driving while taking cannabinoids is a cause for concern, and although driving impairment has been shown to be only moderate, the interaction with alcohol, which impairs driving ability significantly, is particularly worrying. The 'hangover' effect seems to be reasonably weak. Other problems attributed to cannabis include gynecomastia, impairment of fetal growth, and a reduction in fertility and immune function. It has been estimated that around 1 in 10 persons who ever use cannabis will become dependent [27]. An interaction with opioids has been postulated, in that cannabinoids may increase the synthesis or release of endogenous opioids, and may upregulate opioid gene expression in brain and spinal cord areas and regions which regulate pain sensation, motor activity, and pituitary secretion [11]. In a systematic review of safety studies of medical cannabinoids evaluating 23 randomized controlled trials and 8 observational studies, 4,779 adverse events were reported, of which 4,615 (96.6%) were not serious. The serious events included relapse of multiple sclerosis (21 events, 12.8%), vomiting (16 events, 9.8%), and urinary tract infection (15 events, 9.1%) [28]. In a study of brain neuroimaging, 59 long-term heavy cannabis users who started use before age 18 were compared to 33 matched controls. Participants underwent diffusion-weighted magnetic resonance imaging and brain connectivity mapping. Axonal connectivity was found to be impaired in chronic users. The authors concluded that delaying the age at which regular use begins may protect from brain damage [29]. In the Dunedin Study, a cohort of 1,037 individuals was followed from birth (1972/1973) to age 38 years. Cannabis use was ascertained in interviews at ages of 18, 21, 26, 32,

and 38 years. Neuropsychological testing was conducted at age 13, before initiation of cannabis use, and again at age 38. The study demonstrated that persistent cannabis use was associated with neuropsychological decline, and the impairment was concentrated among adolescent-onset cannabis users [30]. On the other hand, a meta-analysis of the effect of cannabis use on global neurocognitive performance showed no significant effect after 25 days of abstinence, concluding that any negative effects of cannabis on neurocognitive performance are attributable to either cannabis residue in the body or withdrawal symptoms, and not to irreversible brain damage [31].

Effects on the GI Tract

Cannabinoid receptors are present throughout the GI tract, including liver, pancreas, stomach, and the small and large intestines. Both CB1 and CB2 receptors are found on enteric neurons, nerve fibers, and terminals throughout the enteric nervous system. CB1 receptors were found on the normal and inflamed human colonic epithelium. Both CB1 and CB2 receptors were found in macrophages and plasma cells in the human colon [29]. General pharmacological action of cannabis consumption on the GI tract includes decreased motility, secretion, and gastric/colonic emptying as well as anti-inflammatory actions [32]. These properties can well explain why cannabinoids seem to have a beneficial effect on inflammatory bowel disease (IBD).

Experimental Animal Models

Cannabinoids were shown to be beneficial in many trials on different models of IBD, some of which are summarized in table 1. The studies have consistently shown that treatment with cannabinoids or cannabinoid agonists reduced inflammation whereas cannabinoid antagonists or cannabinoid receptor knockout increased inflammation.

Human Data

Despite many anecdotal reports on cannabis use in human IBD, there are very few controlled trials. In a survey of 291 patients with IBD who used cannabis, most patients reported using cannabis to ameliorate pain, although ulcerative colitis patients used it also to improve diarrhea. This study, however, was directed to the observation of side effects rather than disease activity. Severe side effects were observed in approximately one third of patients. These included paranoia (32%), anxiety (30%), and palpitations (30%) [41]. It is noteworthy that this study reported an exceptionally high rate of side effects that was not described in any other study, including a meta-analysis of side effects in 1,700 patients using medical cannabis [28]. This high occurrence of side effects may be attributable to the fact that 50% of the patients used cannabis not for their IBD, but for recreation.

In a small study of 13 patients using inhaled cannabis for IBD over a 3-month period, a statistically significant increase in the subject's weight was observed. This was accompanied by an improvement in the disease activity index, perception of general health status, and ability to perform daily activities [42].

We have conducted an observational, retrospective study of 30 Crohn's disease (CD) patients who had a license to use medical cannabis in Israel. Most patients smoked cannabis as 'joints' (0.5 g cannabis/joint) and used between 1–3 joints/day. The Harvey-Bradshaw index decreased from an average of 14 ± 6.7 before cannabis consumption to 7 ± 4.7 ($p < 0.001$). The use of other medications, including 5-aminosalicylic acid, corticosteroids, thiopurine, methotrexate, and TNF antagonists, was also significantly reduced following the use of cannabis [43].

However, in a prospective placebo-controlled study of 19 CD patients, low-dose CBD alone did not show a beneficial effect. The average CD activity index (CDAI) before CBD consumption was 337 ± 108 and 308 ± 96 (p = NS) in the CBD and placebo groups, respectively. After 8 weeks of treatment, CDAI decreased to 220 ± 122 in the CBD group and 216 ± 121 in the placebo group (nonsignificant). No side effects were observed [44]. It should be noted that this study used a very small dose (10 mg/day), whereas several CBD studies have used a dose range between 200 and 800 mg/day in a variety of human diseases [45].

We have recently conducted the first double-blind, placebo-controlled study of THC-rich cannabis inhalation in CD. The study included 21 active CD patients. Complete remission (CDAI score <150) was achieved by 5 of 11 subjects in the cannabis group (45%) and 1 of 10 in the placebo group (10%; $p = 0.43$). A clinical response (a decrease in the CDAI score >100) was observed in 10 of 11 subjects in the cannabis group (90%; from 330 ± 105 to 152 ± 109) and 4 of 10 in the placebo group (40%; from 373 ± 94 to 306 ± 143; $p = 0.028$). Three patients in the cannabis group were weaned from steroid dependency.

Subjects receiving cannabis reported improved appetite and sleep, with no significant side effects. This study, however, is limited by its size and also by the lack of objective measures of disease improvement, such as inflammatory markers [46]. We have, therefore, initiated a larger study which will look into these parameters.

Conclusion

The cannabinoid system has important regulatory functions throughout the human body, including the GI tract, and a major role in the regulation of inflammatory reactions. Despite the importance of the cannabinoid system, it has stayed 'below the radar' of medical research and we are only beginning to discover its implications. Evidence is accumulating showing that manipulation of the endocannabinoid system could have beneficial effects on IBD. However, further research is required before cannabinoids can be declared a medicine. We need to establish the appropriate cannabinoids, as well as medical conditions, dose, and mode of administration for cannabinoid use in IBD.

Disclosure Statement

Lihi Bar Lev is an employee of Tikun Olam organization of medical cannabis. The other authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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