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Medical Cannabis and Cannabinoids

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Medical Cannabis and Cannabinoids: An Option for the Treatment of Inflammatory Bowel Disease and Cancer of the Colon?

Magdalena Grill[a] Carina Hasenoehrl[a] Martin Storr[b, c] Rudolf Schicho[a, d]

[a]Otto Loewi Research Center, Pharmacology Section, Medical University of Graz, Graz, Austria; [b]Department of Medicine 2, Ludwig-Maximilians University, Munich, Germany; [c]Zentrum für Endoskopie, Starnberg, Germany; [d]BioTechMed, Graz, Austria

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Abstract
In the past few years, we have witnessed a surge of new reports dealing with the role of cannabinoids, synthetic as well as herbal, in the mechanisms of inflammation and carcinogenesis. However, despite the wealth of in vitro data and anecdotal reports, evidence that cannabinoids could act as beneficial drugs in inflammatory bowel disease (IBD) or in neoplastic development of the human gastrointestinal tract is lacking. Some insight into the effects of medical *Cannabis* (usually meaning dried flowers) and cannabinoids in IBD has been gained through questionnaires and small pilot studies. As to colorectal cancer, only preclinical data are available. Currently, Δ^9-tetrahydrocannabinol (THC) and its synthetic forms, dronabinol and nabilone, are used as an add-on treatment to alleviate chronic pain and spasticity in multiple sclerosis patients as well as chemotherapy-induced nausea. The use of medical *Cannabis* is authorized only in a limited number of countries. None of the mentioned substances are currently indicated for IBD. This review is an update of our knowledge on the role of cannabinoids in intestinal inflammation and carcinogenesis and a discussion on their potential therapeutic use.

Introduction

The beneficial properties of cannabinoids on the gastrointestinal (GI) tract are built on the fact that the intestines are endowed with the endocannabinoid system (ECS), a regulatory network of cannabinoid receptors, enzymes, and ligands that play key roles in physiological as well as pathophysiological processes [1–4]. Thus, the gut expresses the classical cannabinoid receptors 1 and 2 (CB_1, CB_2) and cannabinoid-responsive non-CB_1/CB_2 receptors (G protein-coupled receptor 55 [GPR55], transient receptor potential cation channel subfamily V member 1 [TRPV1], and peroxisome proliferator-activated receptor gamma and alpha [PPARγ and PPARα]). Further,

M. Grill and C. Hasenoehrl contributed equally to this article.

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Rudolf Schicho
Otto Loewi Research Center, Pharmacology Section
Medical University of Graz, Universitätsplatz 4/I
AT–8010 Graz (Austria)
E-Mail rudolf.schicho@medunigraz.at

endocannabinoid (EC)-producing enzymes, such as N-acyl phosphatidylethanolamine-specific phospholipase D and diacylglycerol lipase, and EC-degrading enzymes, such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), are found in the gut. CB_1 and CB_2 localize mainly to enteric nerves, the intestinal epithelium, and immune cells with variable expression [5–7]. While CB_1 is expressed at high levels on cholinergic enteric neurons [8], CB_2 is largely expressed on immune cells [9].

Anandamide (AEA) and 2-arachidonoylglycerol (2-AG) are the best described ECs which activate CB_1, CB_2, and the abovementioned non-CB_1/CB_2 receptors [10–12]. In addition to these ECS components, EC-like lipids, mostly N-acylethanolamines like palmitoylethanolamide (PEA) and oleoylethanolamide, were found in the GI tract. There, they act on non-CB_1/CB_2 receptors like GPR55 and GPR119 and influence the signaling of AEA, also called "entourage effect" [13]. ECs are most likely involved in numerous regulatory mechanisms, e.g., keeping the epithelial barrier intact [14, 15] and maintaining immune tolerance through controlling the expansion of the regulatory T cell subset Tr1 and the presence of immunosuppressive $CX3CR1^{hi}$ macrophages [16]. Not unexpectedly, changes in the levels of ECs and EC-like lipids have been reported in patients with inflammatory bowel disease (IBD) [17] and colorectal cancer (CRC) [18]. However, it is unknown whether these changes actually correlate with the disease progress. With regard to CRC, in vitro data from colon cancer cell lines convincingly show antiproliferative effects of cannabinoids [19] and, in fact, models of CRC in knockout mice suggest an anti-oncogenic role for at least CB_1 [20, 21]. With regard to CB_2, however, studies in human CRC patients show that its expression correlates with a decreased survival [22]. In a similar way, CB_1 expression was shown to correlate with a poorer survival rate in stage II microsatellite stable CRC [23]. The reports from human and experimental studies, therefore, are controversial concerning a beneficial role of the ECS in CRC. The following chapters briefly summarize the latest results on the role of the ECS and the action of cannabinoids in IBD and CRC, followed by a discussion of a potential therapy with cannabinoids.

Cannabinoids and IBD

IBD, of which ulcerative colitis and Crohn's disease (CD) are major manifestations, is characterized by chronic and relapsing inflammatory attacks of the GI tract [24]. Although the detailed mechanisms are still unknown, an uncontrolled and misdirected immune response against microbial antigens combined with genetic predisposition and environmental factors contribute to the multifactorial appearance of the disease [24, 25].

Insights from Animal Models

Functional data to study the role of the cannabinoid receptors and the ECS in IBD are mainly received from animal models, and they have shown that ECS components are altered during experimental intestinal inflammation. Thus, the reports on increased levels of CB_1, CB_2, and AEA suggest an enhanced cannabinoid signaling under inflammatory conditions [26–28]. Pharmacological activation of CB_1 and CB_2 attenuates experimental colitis [28–30], while the use of antagonists or genetic ablation of the cannabinoid receptors aggravates inflammation [26, 31]. Furthermore, genetic deficiency in FAAH or inhibition of FAAH or MGL (and consequently an increase in AEA or 2-AG) proved to be protective against colitis induced by dextran sulfate sodium (DSS) or trinitrobenzene sulfonic acid (TNBS) [31–36].

Several phytocannabinoids as well as synthetic analogs and EC-like compounds have revealed beneficial effects in animal models of intestinal inflammation. The psychotropic Δ^9-tetrahydrocannabinol (THC) and the nonpsychotropic cannabidiol (CBD) reduced TNBS-induced colitis in the rat colon [37]. Contrary to THC, CBD has extremely low affinity for CB_1 and CB_2, but was shown to have antagonistic effects on GPR55 [11]; CBD was described to act on PPARγ [38] and TRPV1 and to inhibit FAAH activity, thereby altering EC levels [39, 40]. It was also shown to exert protective effects in the dinitrobenzene sulfonic acid (DNBS)-induced colitis model in mice [41]. More recent work demonstrated that a *Cannabis sativa* extract with high content in CBD rather than CBD alone exerts protection [34]. The CBD analog O-1602, which also lacks affinity to CB_1 and CB_2, but which has agonistic properties on GPR55 [11], was shown to have anti-inflammatory effects in colitis; however, these were not mediated by GPR55 [42]. O-1602 seems to mediate reduction of colonic motility via GPR55 [43]. Work in our own laboratory revealed that GPR55 may be a pro-inflammatory actor since a GPR55 antagonist and the genetic deletion of the GPR55 gene ameliorated DSS colitis in mice [44]. Cannabigerol, a nonpsychotropic phytocannabinoid, was shown to improve murine colitis and to reduce nitric oxide production in macrophages and reactive oxygen species formation in intestinal epithelial cells [45]. Another anti-inflammatory and nonpsychotropic

phytocannabinoid is cannabichromene, which was shown to inhibit EC inactivation [46].

The synthetic, nonselective CB_1/CB_2 agonist WIN 55,212-2 was recently tested in DSS-induced colitis and showed protective and anti-inflammatory properties that seem to be at least partially mediated via inhibition of p38 mitogen-activated protein kinase [47]. Another nonselective cannabinoid receptor agonist recently tested in DSS-induced colitis is HU210 [48]. Previously shown to be protective in the DNBS-induced colitis model [26], this substance maintained the integrity of intestinal barrier function independent of Toll-like receptor 4, but produced extraintestinal anti-inflammatory effects that were dependent on Toll-like receptor 4-mediated p38 mitogen-activated protein kinase activation [48].

The EC-like compound PEA is endogenously produced upon an inflammatory insult and has been described to act through CB_1, CB_2, GPR55, PPARα, and TRPV1 [49]. In several chemically induced colitis models in mice, PEA has been shown to reduce inflammation [49, 50] and to protect intestinal permeability via PPARα, CB_2, and GPR55 [49]. In line with these results, inhibition of the PEA-degrading enzyme N-acylethanolamine hydrolyzing acid amidase increased PEA levels and also protected against colitis [51]. Furthermore, Sarnelli et al. [52] reported that inhibition of inflammation-associated angiogenesis by PEA in a DSS model was dependent on PPARα. Additionally, they showed that the release of vascular endothelial growth factor and the formation of vessels were decreased, leading to a reduction in mucosal damage [52]. Recently, the PEA analog adelmidrol was found to exert anti-inflammatory effects that were partly mediated via PPARγ [53].

In summary, although detailed downstream mechanisms of actions of all these compounds are still missing, preclinical data are promising and suggest that synthetic and herbal cannabinoids, FAAH and MGL inhibitors (and consequently increased levels of ECs and EC-like lipids) may be useful to treat IBD. Nevertheless, it will be challenging to find a targeted treatment especially for long-term use with little side effects, considering that the ECS is present in various tissues throughout the body and is involved in many physiological processes.

Cannabinoids and CRC

Observations of altered expression levels of ECS components in tumor biopsies point at a crucial role of the ECS in the development of CRC. Levels of AEA and 2-AG as well as of the enzymes responsible for the synthesis and degradation of ECs were increased in CRC lesions, indicating increased EC metabolism [18, 54, 55]. However, compared to adjacent nonneoplastic colonic mucosa, CB_1 expression was found to be downregulated in CRC samples as a consequence of DNA hypermethylation of CpG islands in the promoter region of *CNR1* (the gene coding for CB_1) [20, 21, 56]. Over the last years, a plethora of preclinical studies has been published, reporting possible antitumorigenic properties of (endo-)cannabinoids including antiproliferative, pro-apoptotic, anti-angiogenic, antimigratory, and anti-invasive properties. The molecular mechanisms by which cannabinoids exert their anticarcinogenic effects have been summarized in great detail elsewhere [57–60]. While data from cell-based assays appear very promising, data obtained from in vivo models are scarcer and paint a rather complicated picture. For instance, treatment with the nonselective CB_1/CB_2 agonist HU210 or CBD reduced the development of precancerous lesions in mouse models of chemically induced CRC [61, 62]. Similar results were obtained by increasing the levels of ECs by way of inhibiting the degrading enzymes FAAH and MGL [61, 63]. However, another study reported that blockade of ECS signaling by application of the CB_1 antagonist SR141716 also reduced preneoplastic lesion formation in a mouse model of CRC [64].

Recently, it has also been brought to light that GPR55, an atypical cannabinoid receptor responsive to certain (endo-)cannabinoids, exerts tumor-promoting effects by increasing tumor burden and metastasis in mice [21, 65]. This highlights the notion that the ECS and its related components exert diverse and often opposing functions and that a better understanding of the underlying mechanisms and interactions of the receptors is essential. For instance, it will be necessary to obtain more information on their effects on the immune cell population associated with tumors, i.e., the tumor microenvironment, before cannabinoids can be transferred to the clinic. With cancer immunotherapy now being introduced even for solid tumors [66], it is rather distressing that only a handful of studies have looked at the effects of cannabinoids on the tumor microenvironment as of now. WIN 55,212-2 (a nonselective CB_1/CB_2 agonist) and JWH133 (a CB_2-selective agonist) were reported to have more pronounced antitumor effects on human melanoma xenografts in immunocompetent mice than on those engrafted into SCID mice [67], indicating that antitumorigenic effects by (endo-)cannabinoids are mediated, partly, via immune cells. Another

study, however, showed that THC suppressed host immune reactivity against lung cancer in mice, thereby promoting tumor growth [68]. This finding was corroborated by Hegde et al. [69], who reported that THC administration caused a massive expansion of myeloid-derived suppressor cells, a heterogeneous cell population with potent immunosuppressive properties. Additionally, we have recently shown that the composition of the immune cells present in colorectal tumors of GPR55-deficient mice was altered compared to that in wild-type mice [21].

In conclusion, it seems that the effects of (endo-)cannabinoids in cancer are much more diverse than currently estimated from the promising in vitro data. Therefore, we may need more thorough basic research on the interactions of the ECS with the tumor immune compartment before embarking on clinical trials with cannabinoids or medical *Cannabis* as an anticancer treatment.

Are Cannabinoids a Therapeutic Option for Inflammation and Neoplasm of the GI Tract?

Cannabis/*Cannabinoids in IBD*

The inflamed gut is highly amenable to treatment with cannabinoids, which is documented for human IBD not only by anecdotal reports but, importantly, also by several questionnaire studies [70–73] as well as observational studies and prospective clinical trials [74–77]. Many of the questionnaires have revealed that patients with IBD frequently self-medicate with *Cannabis* to alleviate abdominal pain and diarrhea. However, long-term use of *Cannabis* may not always be beneficial. A survey by Storr et al. [72] showed that *Cannabis* use for more than 6 months was a strong predictor for surgery in patients with CD. Prospective studies also reported mixed results on the efficacy of cannabinoid treatment in patients with IBD. While a small trial in 21 subjects with CD revealed that short-term application (8 weeks) of THC-rich *Cannabis* caused a decrease in Crohn's Disease Activity Index scores in almost all patients [76], another trial showed that a 2-month treatment in moderate CD with the non-psychoactive CBD was not beneficial [78]. Additionally, experiments on human colonic tissues were performed that provide information on whether cannabinoid-based therapy for IBD would be helpful. By using tissue samples of colon from IBD patients and of appendices, Couch et al. [79] demonstrated that incubation with CBD and PEA prevented inflammatory cytokine production via CB_2 and TRPV1 pathways and via PPARα, respectively. Another study using explants from IBD patients showed that *Cannabis* extract suppressed cyclooxygenase-2 and metalloproteinase-9 expression [80]. The authors described Δ^9-tetrahydrocannabinolic acid as an active non-psychotropic anti-inflammatory ingredient of the extract that could be useful for the treatment of IBD instead of CBD.

Taken together, these studies suggest that treatment with *Cannabis* and cannabinoids indeed may alleviate inflammation in IBD, but most likely this is dependent on dosage, mode of application, and consequently the tissue concentration that can be achieved with cannabinoids. As a downside, however, treatment with cannabinoids that activate the CB_1 receptor come with psychotropic side effects. THC and its derivatives may cause dizziness, somnolence, euphoria, and hallucinations as a result of CB_1 activation in the brain [81]. This problem might be circumvented by using peripherally acting cannabinoids, a strategy that seems highly plausible considering the prominent presence of the ECS in the gut. However, GI motility is strongly influenced by central CB_1 [82], and peripherally restricted agonists to CB_1/CB_2 that were applied intraperitoneally failed to improve inflammation in experimental models of intestinal inflammation [83, 84]. Instead, they were protective when applied intracerebroventricularly [84]. In addition, CB_1 deficiency in the vagal nerve slowed GI motility [85]. These observations indicate that peripheral activation of cannabinoid receptors may not be sufficient for improvement of GI inflammation and that central activation of cannabinoid receptors is necessary for a full healing process. The gut-brain axis may play an important role in this process as well.

Another option to minimize psychotropic adverse effects when treating GI inflammation may be by choosing a lower dose of cannabinoids. From preclinical studies it is known that low-dose application of THC has improving effects on, e.g., atherosclerosis [86] and cognitive function [87]. In patients with chronic upper motor neuron syndrome, treatment with 1 mg/day of nabilone significantly decreased pain [88]. Importantly, nabilone was well tolerated in this study. A clinical trial in elderly patients with dementia also revealed that low-dose THC (0.75 mg twice per day) was safe and well tolerated; there were no differences in feeling "high" between the drug and placebo groups [89]. Because of the prominent expression of CB_1 in the brain, enteric nervous system, and intestinal epithelium, low-dose treatment with cannabinoids in IBD may activate cannabinoid receptors both centrally and peripherally, thus contributing to wound

healing, restoration of barrier function, and relaxation of the gut.

Finally, inhibitors of EC-degrading enzymes raise EC levels and are suitable for the treatment of GI inflammation. Based on preclinical results, MGL inhibitors may be promising candidates for the treatment of IBD [32], but also FAAH inhibitors have proven effective in alleviating experimental intestinal inflammation [35]. However, translation of these effects into human GI disease is lagging behind, especially for FAAH inhibitors, as clinical trials were put on halt since the incident with BIA 10-2474 [90]. In addition, the possibility of cardiovascular side effects of FAAH inhibitors might also limit their use in humans [91–93].

Cannabis/*Cannabinoids in CRC*

Beneficial effects of cannabinoids in CRC are only known from experiments in mice. Knockout of CB_1 in $Apc^{Min/+}$ and C57BL/6 mice [20, 21] causes, depending on the model used, increased tumor burden in the small intestines and the colon, indicating a tumor suppressor role of CB_1 in CRC. In contrast, CB_2 has been implicated in the progression of CRC [22, 94], making it difficult to establish a clear rationale for cannabinoid treatment in human CRC. More preclinical data on the role of CB_2 in experimental CRC are therefore necessary to create a basis for the translation of experimental results into the clinic. Since cannabinoids have been approved for the treatment of emesis and nausea in cancer patients undergoing chemotherapy, we may find out from observations in these patients whether anti-emetic cannabinoid treatment influences cancer progression during chemotherapy. In this context, it should be mentioned that a combination of THC with CBD effectively increased cell death and migration of multiple myeloma cell lines in synergy with carfilzomib, a proteasome inhibitor, used for the treatment of multiple myeloma [95]. The topic of cannabinoid therapy in CRC has also been addressed in a recent editorial [63].

Conclusion

Experimental models of intestinal inflammation demonstrate that treatment with cannabinoids may be helpful. Also in experimental models of CRC, CB_1 was shown to be protective. As to the mechanisms of action, however, it is known that cannabinoids can signal through multiple pathways, most likely in a ligand-biased fashion [96]. Despite the overwhelming amount of data that cannabinoids have anticarcinogenic properties in vitro, in vivo data to support their actions are scarce. Some cannabinoid-responsive receptors, such as GPR55, even have shown pro-inflammatory and procarcinogenic properties. Thus, because of the complexity of mechanisms within the ECS, a beneficial effect of phytocannabinoids and synthetic cannabinoids in humans is not always certain. Additionally, the psychotropic effects of THC and synthetic CB_1 agonists still hamper their broader use, which could be avoided by strategies such as using low-dose cannabinoids with minimal central effects or using peripherally acting cannabinoid receptor ligands. Each approach comes with drawbacks and many questions. Certainly, large clinical studies are needed to create robust guidelines on the safety, effectiveness, dosage, route, form of application, and side effects of cannabinoids. Hopefully, in the near future, clinical data will provide a basis whether *Cannabis* or cannabinoids may become valuable drugs at least for IBD. For CRC, this will certainly take more time.

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Disclosure Statement

The authors have no conflict of interest to disclose.

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