Published in final edited form as:
Neurogastroenterol Motil. 2016 December ; 28(12): 1765–1780. doi:10.1111/nmo.12931.

The gastrointestinal tract – a central organ of cannabinoid signaling in health and disease

Carina Hasenoehrl[1], **Ulrike Taschler**[1], **Martin Storr**[2], and **Rudolf Schicho**[1]

[1]Institute of Experimental and Clinical Pharmacology, Medical University of Graz, Graz, Austria

[2]Department of Medicine, Ludwig-Maximilians University, Munich, Germany and Zentrum für Endoskopie, Starnberg, Germany

Background and Purpose

In ancient medicine, extracts of the marijuana plant *Cannabis sativa* were used against diseases of the gastrointestinal (GI) tract. Today, our knowledge of the ingredients of the *Cannabis* plant has remarkably advanced enabling us to use a variety of herbal and synthetic cannabinoid compounds to study the endocannabinoid system (ECS), a physiologic entity that controls tissue homeostasis with the help of endogenously produced cannabinoids and their receptors. After many anecdotal reports suggested beneficial effects of *Cannabis* in GI disorders, it was not surprising to discover that the GI tract accommodates and expresses all the components of the ECS. Cannabinoid receptors and their endogenous ligands, the endocannabinoids, participate in the regulation of GI motility, secretion, and the maintenance of the epithelial barrier integrity. In addition, other receptors, such as the transient receptor potential cation channel subfamily V member 1 (TRPV1), the peroxisome proliferator-activated receptor alpha (PPARα) and the G-protein coupled receptor 55 (GPR55), are important participants in the actions of cannabinoids in the gut and critically determine the course of bowel inflammation and colon cancer. The following review summarizes important and recent findings on the role of cannabinoid receptors and their ligands in the GI tract with emphasis on GI disorders, such as irritable bowel syndrome, inflammatory bowel disease and colon cancer.

Keywords

Cannabis; cannabinoid receptors; colon cancer; GPR55; IBD; IBS

The endocannabinoid system in the GI tract

Cannabis has a long history as a traditional therapeutic agent for the treatment of abdominal pain and gut dysfunction. This beneficial effect is based on the fact that the gastrointestinal (GI) tract is endowed with cannabinoid (CB) receptors and their endogenous ligands. Together they make up the endocannabinoid system (ECS), a physiologic entity that controls

Author contributions
All authors participated in the writing of the manuscript.

Disclosures
The authors declare no competing interests.

Europe PMC Funders Author Manuscripts

homeostasis in the gut. There is also a wide range of cannabinoid compounds of exogenous origin. Next to herbal cannabinoids, such as Δ^9-tetrahydrocannabinol (Δ^9-THC), cannabidiol, tetrahydrocannabivarin, cannabichromene, cannabigerol and others, there is a large array of synthetic cannabinoids. In general, cannabinoid compounds can be divided into five distinct classes, i.e. classical cannabinoids (e.g., Δ^9-THC); non-classical cannabinoids (e.g., CP-55,940); indoles (e.g., WIN55,212), eicosanoids, and antagonist/inverse agonists (e.g., rimonabant) (1). For a detailed description of the ECS in the gut, the reader is referred to more comprehensive reviews (2,3).

In short, the ECS consists of the CB receptors 1 and 2 (CB_1, CB_2), their endogenous ligands ("endocannabinoids") as well as their degrading and synthesizing enzymes. CB_1 receptors can be found throughout the GI tract. There, they are predominantly located in the enteric nervous system (ENS) (4) and the epithelial lining (5). Additionally, CB_1 is found in extrinsic fibers of the ENS, plasma cells, and in smooth muscle cells of blood vessels within the colonic wall (6,7). Within the ENS, the CB_1 receptor is expressed prejunctionally in cholinergic, but not nitrergic neurons, explaining why CB_1 activation can depress excitatory transmitter release (8). CB_2 receptors are mainly present in immunocytes, myenteric plexus neurons, and in epithelial cells during ulcerative colitis (7,9). In addition to CB receptors, the orphan G-protein coupled receptor 55 (GPR55) and the transient receptor potential cation channel subfamily V member 1 (TRPV1) are endocannabinoid-responsive receptors and may be responsible for non-CB_1/CB_2 receptor effects of cannabinoids in the GI tract and are therefore regarded as part of an expanded ECS (10,11). PPAR receptors, in particular PPARα and PPARγ, are also responsive to herbal, synthetic and endogenous cannabinoids and may mediate many of the analgesic and anti-inflammatory effects observed in cannabinoid treatment [rev. in (12)]. The abovementioned receptors are present in the GI tract, e. g. on nerve terminals of extrinsic primary afferents (TRPV1) (2), and the ENS and enterocytes (PPARα, GPR55) (2,13).

Endocannabinoids are short-lived bioactive lipids and produced "on demand". Arachidonoyl ethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) are among the best characterized endocannabinoids and are synthesized by N-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) and diacylglycerol lipases (DAGL), respectively. They are degraded by specific enzymes: anandamide primarily by fatty acid amide hydrolase (FAAH) and 2-AG by monoglyceride lipase (MGL; or monoacylglycerol lipase, MAGL) (rev. in (3)). In the GI tract, FAAH and MGL were shown to be expressed in epithelial cells, the ENS, and in immune cells during ulcerative colitis (6,7,14). Endocannabinoids may be also degraded by cyclooxygenase-2 (COX-2) and lipoxygenase to give rise to prostaglandin ethanolamides, glyceryl prostaglandins, hydroxyeicosatetraenoic acid and hydroperoxyeicosatetraenoic acid derivatives (15,16). In contrast to the degrading enzymes, the synthesizing enzyme of anandamide, NAPE-PLD, and of 2-AG, DAGL α and β, have been observed in epithelial, myenteric plexus and lamina propria cells, and also in the smooth muscle layer (7).

Acylethanolamides other than anandamide, like palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), can be classified as endocannabinoid-like compounds. They do not directly activate CB receptors but they can activate GPR55 (predominantly PEA) and

GPR119 (only OEA) and are able to influence the signaling of anandamide via an entourage effect (17). PEA and OEA also activate PPARα and are present in high levels within the gut. Both of them are degraded by FAAH, however, PEA is preferentially degraded by another amidase, N-acylethanolamine-hydrolyzing acid amidase (NAAA), which is strongly expressed in immune cells and active particularly in the intestine, suggesting a potentially pathophysiological role in the GI tract (rev. in (17)). In summary, the GI tract is able to locally produce its own endocannabinoid ligands according to its physiological needs and may rapidly react to disturbances in the gut to maintain homeostasis.

Cannabinoids in GI motility and secretion

Cannabinoids affect gut motility mainly by activating CB_1 receptors present on enteric neurons (18). Activation of CB_1 receptors results in the inhibition of acetylcholine release which consequently causes a decrease of intestinal smooth muscle contractility and peristalsis (19). Early studies demonstrated that the plant-derived CB receptor agonist Δ^9-THC, the main component of *Cannabis*, decreases intestinal transit and inhibits electrically evoked contractions in guinea pig explants (20,21). Synthetic CB receptor agonists likewise reduce gastric emptying, upper GI transit, and colonic propulsion (reviewed in (2)). In contrast, rimonabant (SR141716), an inverse agonist of CB_1 receptors, increased electrically-evoked contractions and peristalsis in isolated intestinal segments (22,23), as well as intestinal motility *in vivo* (24). Although CB_2 receptors are expressed in the ENS, they are suggested to play a minor role in the regulation of gut motility under basal conditions but might become important under pathophysiological settings (9). Indeed, JWH-133, a CB_2 receptor agonist, but not arachidonyl-2'-chloroethylamide (ACEA), a CB_1 receptor agonist, attenuated gut transit dose-dependently in the inflamed gut of rats, an effect that was prevented by a CB_2 receptor antagonist (25). There is also increasing evidence that GPR55 is involved in the regulation of gut motility since its agonist O-1602 was able to slow down whole gut transit in mice (13). Both PEA and OEA inhibit intestinal transit in mice but the mode of action is unclear because neither CB receptors nor PPARα seem to be involved in that process (26,27); however, in a mouse model of postinflammatory IBS (mustard oil-induced), inhibition of transit by PEA could be blocked with a CB_1 receptor antagonist, but was not significantly modified with a PPARα antagonist (28).

Acute inhibition of endocannabinoid-synthesizing or - degrading enzymes also modulates intestinal motility. Thus, inhibition of DAGLα was able to normalize gut motility in a mouse model of genetically-induced constipation (29). Pharmacological inhibition of FAAH or MGL led to a decrease in gut motility through mechanisms that involved a rise in anandamide or 2-AG levels, respectively, and the activation of CB_1 receptors (14,30,31). Interestingly, FAAH-deficient mice did not show alterations in basal gut motility; however, pharmacological inhibition or genetic deletion of FAAH normalized endotoxin-induced hypermotility (31). Taschler et al. demonstrated that MGL-deficient mice did not show alterations in basal gut motility but that they were insensitive to CB receptor agonist treatment due to desensitization of intestinal CB_1 receptors (30).

It has to be noted that also the gut brain-axis may account for the regulation of gut motility by cannabinoids. For instance, intracerebroventricular injection of the CB receptor agonist

WIN55,212-2 attenuated whole gut transit in mice (32). Additional evidence that gut motility might be regulated by central CB receptors was provided by Vianna *et al.* who showed that deletion of CB_1 receptors specifically in the vagal nerves of mice caused an increase in GI motility (33). Similar to rodents, CB_1 receptors are functionally present in the human small and large intestines (34–36). Thus, WIN55,212-2 and ACEA inhibited electrically-evoked contractions in a healthy human colon and this effect was completely blocked by rimonabant (37). Also 2-AG and anandamide were shown to inhibit acetylcholine-induced contractions in explants of human colonic longitudinal and circular muscle, however, this effect could not be blocked with CB_1 or CB_2 antagonists (38). The authors suggested a non-cannabinoid or alternative cannabinoid pathway mediating this effect (38). It is possible that the non-CB effects by anandamide may have been brought about by GPR55 which causes relaxation in the murine colon (13).

There is evidence that cannabinoids play an important role in the regulation of gastric and intestinal secretion in rodents and humans. Studies revealed that cannabinoids reduce the production of gastric acid secretion by activating CB_1 receptors (19). In mice, intestinal hypersecretion induced by cholera toxin was reduced by CB_1 receptor activation (39). In another study, pharmacological inhibition or genetic deletion of FAAH provided beneficial effects against diclofenac-induced gastric irritation (40). In contrast, enhanced secretion was observed in humans treated with the CB_1 antagonist rimonabant (41). In summary, a large body of evidence demonstrates that (endo-) cannabinoids affect physiologic functions of the gut, a property that could be therapeutically exploited. Activation of CB_1 receptors by increased levels of endocannabinoids and, as a consequence, a slowed gut motility might have beneficial effects for patients with symptoms of hypermotility. On the other hand, inhibition of endocannabinoid synthesis or blockade of CB_1 receptors might enhance gut motility in GI disorders associated with constipation. If central side effects of cannabinoids could be overcome, modulation of cannabinoid levels would certainly represent a valuable pharmacological approach for the treatment of GI disorders. Another possibility could be the use of non-psychotropic cannabinoids like cannabidiol, which has been described as a ligand of many receptors including GPR55, TRPV2, PPARγ and 5-HT1A but not of CB receptors (but might modulate their actions) (42). Cannabidiol has shown relaxant effects on croton oil- and sepsis-induced hypermotility in mice (43,44).

Cannabinoids in emesis and nausea

The dorsal vagal complex (DVC) in the brainstem is the site responsible for the vomiting reflex while the neural circuitry responsible for nausea is less known. CB receptors and particularly FAAH and MGL are present in the DVC and area postrema suggesting an important role of endocannabinoids in the control of emesis (45–47). Cannabis has been traditionally used as an antiemetic agent, and exogenous cannabinoids are presently prescribed for people with chemotherapy-induced nausea and vomiting (48). However, due to central side effects, cannabinoids are not used as first line drugs.

The endocannabinoids anandamide and 2-AG have been shown to reduce emesis in experimental models (46). Drugs that can raise endocannabinoid levels without causing the typical cannabinoid agonist-induced central side effects are therefore potential options to

treat emesis. The FAAH inhibitor URB597 reduced LiCl-induced emesis via CB_1 and CB_2 receptors (46). Reduction of emesis by the MGL inhibitor JZL184 was shown to be sensitive to CB_1 antagonism (49). Also cannabidiol showed anti-emetic and anti-nausea effects in animal models, the effects were brought about by indirect agonism of $5\text{-}HT_{1A}$ somatodendritic autoreceptors in the dorsal raphe nucleus (50).

The role of endocannabinoids has been investigated more recently in detail in the conditioned gaping model in rats and results indicate that 2-AG and the visceral insular cortex (VIC) could play an important role in nausea (51). Exogenous 2-AG, but not exogenous anandamide, applied by bilateral intra VIC infusion, dose-dependently suppressed conditioned gaping (51). The effect could not be blocked with the CB_1 antagonist AM251, but instead with the COX inhibitor indomethacin (51). Interestingly, bilateral VIC infusion with the MGL inhibitor MJN110 also suppressed conditioned gaping but here, the effect could be blocked with AM251 (52).

Endocannabinoids have been clearly established as important messengers in the neuronal network that controls vomiting and nausea. Interference with endocannabinoid degradation may represent a valuable therapeutic approach not only against emesis but also against anticipatory nausea in chemotherapy patients.

Cannabinoids and functional bowel disorders

Irritable bowel syndrome (IBS) and functional dyspepsia are the most frequent functional bowel disorders encountered globally. The previous view that functional GI disorders lack histopathological and biochemical alterations has been challenged by studies demonstrating low grade inflammation, increased presence of immune and mast cell, changes in the epithelial barrier, and bacterial overgrowth in IBS patients. These alterations together with a derangement of the gut-brain axis may be involved in the development of visceral hyperalgesia and motility disturbances. The predominant presence of CB_1 receptors along the gut-brain axis may allow cannabinoids to positively influence derangements along this axis (3,53). The role of the ECS in IBS has been already described in a previous review by Storr&Sharkey (53). Here, more recent results will be summarized and discussed.

IBS: visceral hypersensitivity and the ECS

Symptoms of IBS, such as abdominal pain, discomfort, and altered bowel habits, have been previously linked with visceral hypersensitivity and aberrant 5-hydroxytryptamine (5-HT) signaling (53). Feng et al. explored the link between 5-HT and the ECS and observed increased levels of 5-HT, but a decrease in anandamide, in the duodenal mucosa of patients with postinfectious IBS (PI-IBS) (54). Using a rat model, they showed that acute luminal administration of 5-HT into the duodenum induced anandamide release via vagal $5\text{-}HT_3$ receptors, whereas chronic 5-HT treatment decreased anandamide levels via $5\text{-}HT_3$, indicating that 5-HT may be involved in the regulation of intestinal anandamide content. In addition, luminally-applied CB_1 receptor agonists attenuated 5-HT-induced hyperalgesia (54). In IBS-D (diarrhea-predominant) patients, no changes in anandamide levels but a decrease in PEA was observed in comparison to healthy subjects. The decrease was associated with abdominal pain (55). The IBS-D patients also had an increase in 2-AG while

IBS-C patients had higher levels of OEA (55). It is interesting that levels of PEA were also found decreased in a mouse model of inflammation-induced hypermotility (croton oil-induced) (56). The decrease was reduced by a non-psychoactive *Cannabis* extract, cannabichromene, in a CB receptor-independent manner (56). In contrast, in a mouse model of postinflammatory IBS (mustard oil-induced), PEA slowed gut transit, an effect that was dependent on CB_1 receptors (28). By use of a trinitrobenzenesulfonic acid (TNBS)-induced model of visceral hypersensitivity, Iwata et al. showed that a CB_2 receptor agonist was effective in improving pain thresholds in a dose-dependent manner without signs of central CB_1 receptor activation (40,57). Considering these data it is possible that low levels of endocannabinoids in IBS patients may contribute to hyperalgesia and abdominal pain and cause perturbations in the bowel motility which could be improved by endo- or exocannabinoids via CB- and possibly non-CB receptor pathways. This leads to the idea that FAAH inhibitors could be valuable therapeutics against PI-IBS and possibly other forms of IBS. In accordance with this concept, several studies reported that pharmacological inhibition of FAAH and also MGL significantly reduced visceral nociception in rodent models of colorectal distension and acetic acid-induced abdominal stretching (40,58,59). In this context it is worth to mention the role of mast cells in IBS. Activated mast cells have been shown to correlate with abdominal pain in IBS (60). Since mast cells express CB receptors and are also targets of PEA (61), which is thought to modulate mast cells activation, endocannabinoids may regulate activity of mast cells and hence interfere with IBS symptoms like abdominal pain; however, this remains to be shown.

IBS: stress, pain and the ECS

Chronic stress can induce visceral hyperalgesia via the hypothalamic–pituitary–adrenal axis and probably adds to the pain that IBS patients perceive. Recent work in rat models has shown that chronic stress causes reciprocal changes in 2-AG and COX-2/FAAH levels in L6–S2, but not L4–L5 dorsal root ganglia (DRGs) (62). Moreover, CB_1 receptors were downregulated while TRPV1 receptors were upregulated in L6–S2 but not in L4–L5 DRGs, indicating region-specific changes in primary sensory fibers innervating the distal colon (62). A report suggests that epigenetic regulation in the DRG neurons could be responsible for these changes: while chronic stress was associated with methylation in the promoter region of the Cnr1 gene (encodes the CB_1 receptor), histone acetylation at the Trpv1 promoter and expression of the TRPV1 receptor were increased (63). These findings point out that reciprocal changes in the endovanilloid and endocannabinoid system occur in visceral sensory fibers and that these changes could contribute to hyperalgesia and abdominal pain.

Stress and visceral pain may be also regulated by the ECS within the CNS. It is known that chronic stress reduces levels of anandamide (but increases 2-AG) in the brain and downregulates CB_1 receptors, and that these changes may contribute to the stress response (64). In line with this, both the FAAH inhibitor PF 3845 and the dual FAAH/MAGL inhibitor JZL 195 were effective in inflammatory and mechanically evoked visceral pain models suggesting that an increase in endocannabinoid levels alleviates visceral pain (59). A more thorough description of this topic is given in (65).

IBS: genetic variations and the ECS

Genetic variations of ECS components (CB receptors, synthesizing/degrading enzymes) may be associated with the pathogenesis of functional bowel disorders. Polymorphism in the *FAAH* gene (C385A) leads to a mutant FAAH enzyme and reduces breakdown of anandamide (66). A study in patients with constipation predominant (C-) IBS, D- and M- (mixed) IBS, with chronic abdominal pain and functional dyspepsia, showed a clear association of the non-wild type *FAAH* genotype with functional bowel disease phenotypes and with accelerated colonic transit in IBS-D patients (67). However, no statistically significant association between the *FAAH* genotype and sensation measurements was observed (67). A polymorphism in the *CNR1* gene, rs806378, was found to be significantly associated with IBS symptom phenotype, colonic transit in IBS-D, and sensation rating of gas, but not with pain (68). In line with a possible role of *CNR1* variants in the development of IBS symptoms, allele frequencies of AAT triplet repeats in *CNR1* were observed to be associated with IBS in a study of a Korean population (69). Similar results, namely the detection of eight *CNR1* alleles with AAT triplet repeats, were reported in a Chinese IBS cohort, whereas no association could be detected between C385A *FAAH* polymorphism and IBS pathogenesis (70). Interestingly, FAAH activity was recently determined in whole colon samples from patients who underwent colectomy for slow transit constipation (71).The results revealed a strong decrease in activity in these patients as compared to individuals free of transit dysfunction (71). The FAAH enzyme, therefore, seems to be a key molecule for the regulation of endocannabinoid levels and colon motility, but not for GI pain sensation.

Effect of CB receptor agonists in IBS patients

From animal studies it was rightfully concluded that cannabinoid agonists could improve visceral pain thresholds in humans. In a previous study performed in healthy volunteers to investigate the effect of dronabinol (Δ^9-THC) on colonic motility and sensation, 7.5 mg dronabinol induced relaxation of colon motility and tone postprandially (72). The effect of dronabinol on visceral perception to rectal distension was then tested in IBS patients (positively diagnosed by Rome II criteria) and healthy subjects in a small trial, but no differences in sensory thresholds and discomfort were observed between the cohorts (73). A different study revealed inhibitory effects of dronabinol on fasting colonic motility and an increase in colonic compliance, particularly in patients with diarrhea predominant forms of IBS, but failed to demonstrate effects on sensation and tone (74). The report also suggested that *FAAH* and *CNR1* variants could have had an impact on the effects of dronabinol (74). In a subsequent trial performed in IBS-D patients, no significant effect of dronabinol on colonic transit was observed; however, in a subset of patients with the *CNR1* polymorphism rs806378, dronabinol moderately delayed colonic motility (75).

Thus, it seems that CB receptor activation in IBS has potential therapeutic value, but probably only in IBS-D patients with genetic variations of ECS components.

Functional dyspepsia

There is good indication that the ECS may be involved in functional dyspepsia. Tack et al. have previously shown that early satiety and symptoms of functional dyspepsia are caused by a disturbed gastric accommodation (76). In addition, hypersensitivity to gastric balloon

distension was observed to be present in a subset of patients with functional dyspepsia (77). A cross-over, randomized, controlled clinical trial in healthy individuals now demonstrated that CB_1 receptor antagonist rimonabant was able to inhibit meal-induced gastric accommodation, but did not affect fasting gastric compliance or sensitivity to gastric balloon distension, indicating that gastric accommodation is controlled by endocannabinoids (78). However, it was not clear from the study whether the ECS controls accommodation via centrally-mediated pathways or via the ENS. A new study has recently addressed the question as to whether CB_1 receptors in the brain are involved in functional dyspepsia and could demonstrate that increased availability to a CB_1 receptor radioligand was predominantly found in brain regions involved in the regulation of visceral pain and satiety (79).These findings would argue for a role of central CB receptors in the regulation of gastric accommodation in humans. It is, therefore, possible that both, central and peripheral CB receptors are involved in the development of functional GI disorders, and that pharmacological manipulation of exclusively peripheral CB receptors may not provide full benefit for patients with these disorders.

Microbiota and the ECS

A change in the microbiotic population of the gut may alter the permeability and lead to metabolic endotoxemia and hence to metabolic disorders associated with obesity. Endocannabinoids are involved in the regulation of energy metabolism and food intake and communicate in this respect with the microorganisms of the gut (80). The epithelial lining expresses CB receptors and they are most likely involved in these mechanisms. 2-AG and PEA cause an increase in epithelial barrier function (“gate keeper”) while anandamide is thought to be a “gate opener” (81). Thus, the intestinal ECS may have an important role in the control of microbial products entering the bloodstream and in the development of metabolic diseases. A detailed review on this topic is given in (81).

Dysbiosis (alteration in the composition of gut microbiota) has been also suggested as one of the potential causes of IBS, especially in the case of PI-IBS (82). It is known that antibiotic therapy provides certain benefits for IBS patients (83), however, it is not quite clear how eradication of bacteria could contribute to symptom relief. In this context it is interesting that *Lactobacillus acidophilus* NCFM could induce CB_2 receptor expression in the rodent gut mucosa (84). When applying NCFM in a model of chronic colonic hypersensitivity, it caused analgesia which was abrogated by i.p. blockade with AM630, suggesting that CB_2 receptors may provide a link between gut microbiota and visceral hypersensitivity (84). However, in a human trial, CB_2 receptors were not found to be upregulated in colonic mucosal biopsies from persons that were given *Lactobacillus acidophilus* NCFM over a period of 21 days (85). On the other hand, treatment of mice with antibiotics reduced pain-related responses to i.p. application of acetic acid or intracolonic capsaicin (86). The effect was accompanied by a small rise in CB_2 receptor transcripts in colon tissue, as well as a decrease of CB_1 and mu-opioid receptors. Additionally, total luminal bacterial counts correlated with CB receptor expression (86) suggesting a possible interaction between microbial products and CB receptors.

Cannabinoids and intestinal inflammation

Chronic inflammatory conditions of the GI tract are known as inflammatory bowel disease (IBD) and occur in two major forms, ulcerative colitis (UC) and Crohn's disease (CD). IBD is thought to originate from a complex interaction of the gut microbiota (or their products) with the epithelial barrier, based on the genetic background and the immune system of the host (87). To investigate the role of cannabinoids in IBD, mostly animal models that rely on chemically-induced mucosal inflammation have been used.

The endocannabinoid system as a therapeutic target in IBD

Evidence gathered from several studies in rodents points to a therapeutic relevance of the ECS in IBD. As reviewed by Izzo & Sharkey (2) and Alhouayek & Muccioli (88), endocannabinoid signaling is largely enhanced in the inflamed intestine. Expression of CB_1 (89) and CB_2 receptors (90), and of anandamide (91) were increased, whereas FAAH levels were reduced in the initial phase of colitis (92). Pharmacological strategies to enhance endocannabinoid levels, either by inhibition of endocannabinoid degradation (92–94) or of the transport across the plasma membrane (91,92) ameliorated inflammation. In particular, inhibition of FAAH by PF-3845 (94) and FAAH/COX blockade by ARN2508 (95) dramatically reduced damage in experimental colitis models. In the latter study, raised levels of anandamide, PEA and OEA were measured that most likely contributed to the beneficial effect (95). A recent work by Alhouayek *et al* showed that inhibition of NAAA, which preferentially degrades PEA, caused significant improvement of experimental colitis suggesting that PEA is an important acylethanolamide in the regulation of intestinal inflammation (96). In accordance, oral administration of PEA (which is interestingly sold as an over-the-counter drug and advertised to mitigate symptoms of GI disorders) exerted anti-inflammatory effects in the gut (97). Experiments on cultured human colonic biopsies derived from UC patients showed that PEA caused a decrease in expression and release of inflammatory mediators which was dependent on PPARα (98).

Activation of the CB_1 (89) or CB_2 receptor (90,99) with specific agonists also protected from colitis. Accordingly, genetic ablation or pharmacological antagonism of CB_1 (89,100) or CB_2 receptors (90,100) left mice more susceptible to intestinal inflammation. Moreover, treatment with Δ^9-THC was reported to reduce colitis in rats (101). The limitations of using *Cannabis* for treatment of gut inflammation, however, are the psychoactive effects that arise from activation of CB_1 receptors in the brain. Investigation of pharmacologically active cannabinoids with low or no affinity for CB_1 receptors and of atypical cannabinoids would be therefore of high interest. Indeed, it has been shown that cannabidiol and cannabigerol, two non-psychotropic ingredients of *Cannabis*, have proven beneficial in various models of intestinal inflammation (101–105). Also, the atypical cannabinoid O-1602 was reported to reduce disease severity in a CB_1-/ CB_2 receptor-independent way by inhibiting neutrophil recruitment (106). Recently, GPR55, which is part of the "expanded" ECS, has been investigated in experimental colitis. A pro-inflammatory role of GPR55 could be established because genetic deletion of GPR55 and treatment with the GPR55 antagonists CID16020046 or ML-191 alleviated intestinal inflammation (97,106,107). In this context, cannabidiol, which is known to act as a GPR55 antagonist (108), showed inhibition of GI inflammation

in an LPS-induced model by targeting enteric reactive gliosis (103). Interestingly, only parts of the beneficial effects of cannabidiol in this model were mediated by PPARγ (103) raising the possibility that GPR55 could have been involved in this effect. Cannabidiol may also exert a protective effect on the intestinal barrier. In a Caco-2 cell monolayer stimulated by EDTA, cannabidiol concentration-dependently caused rapid recovery of the barrier and this effect was inhibited by a CB_1 antagonist (109). Since cannabidiol has no affinity to CB_1 receptors, the authors argued that cannabidiol could have antagonized CB_1-mediated increases in permeability mediated by locally produced endocannabinoids (109). Activation of CB_2 receptors also attenuated cytokine-evoked mucosal damage in human colonic explants (110).

Cannabis for the treatment of IBD?

Questionnaires among IBD patients revealed that *Cannabis* is commonly used as a self-medication to relieve IBD-related symptoms like abdominal pain, diarrhea, and loss of appetite (111,112). A retrospective study reported significant improvements in 21 out of 30 CD patients after *Cannabis* use (113). In a small prospective placebo-controlled study of CD patients, a beneficial clinical response was achieved in 10 out of 11 subjects in the treatment group (114). A more recent questionnaire confirmed that the use of *Cannabis* subjectively improved pain and other symptoms in IBD patients, but also pointed out that *Cannabis* use for more than six months was a strong predictor in CD patients for requiring surgery (115).

Despite these interesting findings, the exact mechanisms how the ECS operates in IBD have not yet been unraveled but evidence gathered so far points to an overall protective role (Fig. 1). The up-regulation of ECS components possibly constitutes an attempt to restore homeostatic balance (3). Cannabinoids have been shown to influence the recruitment of immune cells to the site of intestinal inflammation (93,106,107) and to reduce the release of pro-inflammatory cytokines, i.e. TNF-α, IFN-γ, IL-1β and IL-6 (93,102,103,105). Activation of the CB_1 receptor might also lead to enhanced wound closure during colitis (5). Of particular interest are recent findings that gut microorganisms may influence the expression of intestinal ECS components (81). 2-AG and PEA were mostly associated with beneficial effects on the gut-barrier function (81). The crosstalk between gut microbiota and the ECS is therefore worthy to be further examined in future studies.

Collectively, cannabinoids show great potential in the treatment of IBD and further research is warranted to gain a better insight into the mechanistic actions of (endo-) cannabinoids.

Cannabinoids and colon cancer

Differential expression of components of the ECS in colorectal cancer (CRC) was first reported by Ligresti et al. (116). In this study, anandamide and 2-AG contents were found to be higher (3-fold and 2-fold, respectively) in CRC lesions as compared to normal colonic mucosa and, interestingly, their levels were higher in adenomatous polyps than in carcinomas (116). Increased endocannabinoid synthesis in CRC was also reported in a more recent study (117). Here, anandamide, as well as its synthesizing enzyme NAPE-PLD, were up-regulated approximately 2-fold in cancer tissues. Intriguingly, mRNA expression and activity levels of FAAH were also increased. Most likely, as a consequence of increased

FAAH activity, elevated levels of arachidonic acid, the main product of anandamide and 2-AG degradation, were also detected (117). In another study, the main degrading enzyme of 2-AG, MGL, was also found increased in CRC specimens (118).

Examination of CB_1 expression revealed a down-regulation of mRNA levels in 18 out of 19 colon cancer samples as compared to adjacent non-neoplastic colon mucosa (119). The reason for this silencing was found to be DNA hypermethylation at CpG islands around the transcription start site of *CNR1.* In parallel to the epigenetic regulation, also protein levels of CB_1 receptors were reduced in colon cancer specimens as shown by Western blotting (119). These findings were corroborated by Cianchi et al. who reported CB_1 receptor expression to be higher in normal colonic epithelium than in colonic tumor tissue (120). However, a comprehensive study describing the correlation between CB_1 receptor immunoreactivity and patient outcome conducted in 534 Korean patients found no differences in overall survival between patients with carcinomas of either high or low CB_1 receptor immunoreactivity (121). Distant metastasis was found to be lower in patients with high CB_1 receptor expression, but there were no differences in lymph node metastasis, tumor invasion, or tumor size. Surprisingly, in stage IV patients, high CB_1 immunoreactivity even correlated with a poorer survival rate (121). Similar observations were made in a cohort of 487 Swedish patients (122). There, high CB_1 expression was reported to correlate with poorer disease-specific survival in stage II microsatellite stable CRC patients (122). Reduced overall survival has also been reported for patients who were either homo- or heterozygous for the 1359 G/A single nucleotide exchange in the *CNR1* gene although it is not yet known how this polymorphism affects cannabinoid signaling (123). CB_2 receptor mRNA expression was found in 28.6% of CRC samples and significantly correlated with lymph node involvement (124), however, no consistent data on protein expression were available. So far, the human studies indicate increased endocannabinoid activity in colon cancer while the role of CB receptors remains less clear.

Cannabinoids reduce carcinogenesis in animal models of colon cancer

In mice, colon cancer can be induced either chemically or, for instance, by germline mutation of the adenomatous polyposis coli (*Apc*) gene. $Apc^{Min/+}$ mice spontaneously develop multiple polyps in the intestine. Additional knock out of *Cnr1* or inhibition of the CB_1 receptor with AM251 in these mice caused a strong increase in intestinal polyp burden, whereas activation of CB_1 receptors with methanandamide significantly reduced the number of polyps (119). Genetic deletion of *Cnr2* (the gene encoding CB_2 receptor), had no effect on polyp growth in this model (119). Chemically, colon cancer develops after multiple intraperitoneal injections of the carcinogen azoxymethane (AOM). In this model, anandamide and 2-AG were found increased in the colon of AOM-treated mice (125). In addition, inhibition of FAAH with *N*-arachidonoyl-serotonin (AA-5-HT) reduced the development of precancerous lesions, and furthermore, the non-selective, synthetic CB_1/CB_2 receptor agonist, HU210, was able to mimic this effect (125).

Antitumorigenic effects in the AOM model were also observed with non-psychotropic cannabinoids. For instance, cannabidiol was shown to reduce the formation of aberrant crypt foci (ACF), polyps, and tumors in the colon and the AOM-induced up-regulation of p-Akt

(126). It also counteracted caspase-3 inactivation. In colorectal carcinoma cell lines, it protected DNA from oxidative damage and it reduced cell proliferation in a CB_1-, TRPV1- and PPARγ-antagonists sensitive manner (126). A “cannabidiol botanical drug substance” (a *Cannabis sativa* extract with high content of cannabidiol) had similar effects in the same model, reducing ACF, polyp and tumor formation via CB_1 and CB_2 receptor activation (127), whereas treatment with cannabigerol reduced the number of ACFs only (128). In yet another murine model, in which colitis-associated colon cancer was induced through the application of AOM and dextran sulfate sodium (DSS), the atypical cannabinoid O-1602 showed antitumorigenic properties (129). The drug reduced the number and area of tumors by 30% and 50%, respectively. In addition, activation of the oncogenic transcription factor STAT3 was decreased while pro-apoptotic factors p53 and Bax were increased in O-1602 treated mice (129). Perhaps surprisingly, one study showed that antagonism of CB_1 receptors with rimonabant reduced the formation of ACFs with 4 or more crypts in mice with AOM-induced colon cancer (130).

Potential applications of cannabinoids and related substances have also been studied in xenograft models. The semi-synthetic cannabinoid quinone HU-331 (131) and the hexahydrocannabinol analogue LYR-8 (132) reduced tumor growth of xenografts derived from HT-29 cells. Likewise, the CB_2 receptor agonist CB13 inhibited the growth of DLD-1 derived tumors (120). A “cannabidiol botanical drug substance” (127) and cannabigerol (128) decelerated or even halted the growth of HCT116 xenografts, respectively.

Anticarcinogenic mechanisms of cannabinoids: reduction of cancer cell proliferation and inhibition of angiogenesis and metastasis

Cannabinoids have been shown to exert anti-proliferative effects on colon cancer cells through apoptosis via activation of CB_1/CB_2 receptors, or through receptor-independent mechanisms (rev. in (133)). The molecular mechanisms underlying the induction of apoptosis upon CB_1/CB_2 receptor activation have been discussed in detail by Velasco et al. (134). Briefly, *de novo* synthesis of the pro-apoptotic sphingolipid ceramide (120), down-regulation of the protein survivin (inhibitor of apoptosis) (119), inhibition of PI3K/Akt signaling (135,136), and induction of endoplasmic reticulum stress that leads to autophagy-mediated cell death (136), have all been reported. Notably, cannabinoids with low or no affinity for CB receptors (like cannabidiol and O-1602) are also known to exert anti-proliferative effects, although the underlying mechanisms have not yet been fully clarified (126,127,129). A cannabinoid-like compound LYR-8, for instance, was demonstrated to decrease angiogenesis in a xenograft model using chick chorioallantoic membranes (132). Concomitantly, the expression of factors that modulate the tumor microenvironment, like vascular endothelial growth factor, COX-2, and hypoxia-inducible factor 1α was reduced in this model (132). Inhibition of MGL, either pharmacologically or through silencing with siRNA, attenuated the invasion of colon cancer cells (118), suggesting a role of endocannabinoid degrading enzymes in CRC progression. Importantly, adhesion and migration of highly metastatic colon cancer cells was shown to be diminished after treatment with cannabidiol or a GPR55 inhibitor (108).

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

In conclusion, data obtained so far point to a deregulation of the ECS in colon cancer that could be interpreted as an attempt to restore the original healthy state. Despite controversial data on the role of the ECS in human colon cancer, promising preclinical data on the reduction in tumor growth by typical and atypical cannabinoid compounds warrant further exploration on the cause of ECS deregulation in colon carcinogenesis. It should be of prime interest to investigate known and hitherto unknown components of the ECS to better understand the complexity of CB receptor signaling by endocannabinoids and the regulation of their synthesizing and degrading enzymes.

Concluding remarks

Cannabinoids have a long history of being used to treat diseases or to alleviate symptoms. In modern medicine, this is not fully translated, and cannabinoids or cannabinoid-derived drugs are rarely used mainly due to the lack of clinical trials supporting such use. Over the last decades, cannabinoid research was driven by basic scientists who characterized pharmacological actions of cannabinoids, who discovered the ECS with all its constituents, and who taught us how activation or blockade at different sites may be helpful for the treatment of GI diseases. The GI tract is one of the regions where cannabinoid signaling is involved in many physiological and pathophysiological regulatory mechanisms, this is now clearly understood. The last decade has added more translational studies, and we have learned where cannabinoids are involved in pathophysiological states and human disease and where and how cannabinoids alter physiological or pathophysiological conditions. Through a recent meta-analysis we are also better informed on side effects associated with cannabinoid treatment. The analysis revealed that there was an increased risk of short-term adverse events with cannabinoids, mostly dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, drowsiness, but also cardiac (1.42; 0.58-3.48; odds ratio; 95% CI) and hepatobiliary (3.07; 0.12-76.29; odds ratio; 95% CI) disorders were among them (137). Nevertheless, the opportunities are multifold with targeting the numerous involved receptors with agonists and antagonists, and with targeting synthesizing and degrading mechanisms. To harvest the potential therapeutic effects is now challenging, but based on the broad cannabinoid platform built by basic researchers, clinical trials are urgently wanted. From a scientist’s perspective and all the caveats in mind, it seems to be a matter of time when cannabinoid compounds will be used in the treatment of GI disease

Acknowledgements

Work in the lab of R.S. is supported by the Austrian Science Fund (FWF P25633 and KLI 521-B31). Work in the lab of M.S. is supported by the Deutsche Forschungsgemeinschaft (DFG). CH is a participant of the PhD Program Molecular Medicine at the Medical University of Graz.

Abbreviations

ACEA	arachidonyl-2'-chloroethylamide
ACF	aberrant crypt foci
2-AG	2-arachidonoylglycerol

Europe PMC Funders Author Manuscripts

AOM	azoxymethane
AA-5-HAT	*N*-arachidonoyl-serotonin
CB	cannabinoid
CI	confidence interval
CRC	colorectal cancer
CD	Crohn's disease
COX-2	cyclooxygenase-2
DAGL	diacylglycerol lipase
DRG	dorsal root ganglion
DVC	dosal vagal complex
ECS	endocannabinoid system
ENS	enteric nervous system
FAAH	fatty acid amide hydrolase
GI	gastrointestinal
GPR55	G-protein coupled receptor 55
GPR119	G-protein coupled receptor 119
5-HT	5-hydroxytryptamine
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
MGL	monoglyceride lipase
NAPE-PLD	N-acyl phosphatidylethanolamine phospholipase D
NAAA	N-acylethanolamine-hydrolyzing acid amidase
OEA	oleoylethanolamide
PEA	palmitoylethanolamide
PPARα	peroxisome proliferator-activated receptor alpha
PPARγ	peroxisome proliferator-activated receptor gamma
Δ^9-THC	Δ^9-tetrahydrocannabinol
TNBS	trinitrobenzenesulfonic acid
TRPV1	transient receptor potential cation channel subfamily V member 1

UC ulcerative colitis

VIC visceral insular cortex.

References

1. Console-Bram L, Marcu J, Abood ME. Cannabinoid receptors: nomenclature and pharmacological principles. Progress in Neuropsychopharmacology & Biological Psychiatry. 2012; 38:4–15.
2. Izzo AA, Sharkey KA. Cannabinoids and the gut: new developments and emerging concepts. Pharmacology & Therapeutics. 2010; 126:21–38. [PubMed: 20117132]
3. Schicho R, Storr M. Targeting the endocannabinoid system for gastrointestinal diseases: future therapeutic strategies. Expert Review of Clinical Pharmacology. 2010; 3:193–207. [PubMed: 22111567]
4. Coutts AA, Irving AJ, Mackie K, Pertwee RG, Anavi-Goffer S. Localisation of cannabinoid CB(1) receptor immunoreactivity in the guinea pig and rat myenteric plexus. The Journal of Comparative Neurology. 2002; 448:410–22. [PubMed: 12115703]
5. Wright K, Rooney N, Feeney M, Tate J, Robertson D, Welham M, Ward S. Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. Gastroenterology. 2005; 129:437–53. [PubMed: 16083701]
6. Duncan M, Davison JS, Sharkey KA. Review article: endocannabinoids and their receptors in the enteric nervous system. Alimentary Pharmacology & Therapeutics. 2005; 22:667–83. [PubMed: 16197488]
7. Marquez L, Suarez J, Iglesias M, Bermudez-Silva FJ, Rodriguez de Fonseca F, Andreu M. Ulcerative colitis induces changes on the expression of the endocannabinoid system in the human colonic tissue. PloS ONE. 2009; 4:e6893. [PubMed: 19730730]
8. Boesmans W, Ameloot K, van den Abbeel V, Tack J, Vanden Berghe P. Cannabinoid receptor 1 signalling dampens activity and mitochondrial transport in networks of enteric neurones. Neurogastroenterology and Motility. 2009; 21:958–e77. [PubMed: 19374636]
9. Duncan M, Mouihate A, Mackie K, Keenan CM, Buckley NE, Davison JS, Patel KD, Pittman QJ, et al. Cannabinoid CB2 receptors in the enteric nervous system modulate gastrointestinal contractility in lipopolysaccharide-treated rats. American Journal of Physiology. 2008; 295:G78–87. [PubMed: 18483180]
10. Ross RA. Anandamide and vanilloid TRPV1 receptors. British Journal of Pharmacology. 2003; 140:790–801. [PubMed: 14517174]
11. Schicho R, Storr M. A potential role for GPR55 in gastrointestinal functions. Current Opinion in Pharmacology. 2012; 12:653–8. [PubMed: 23063456]
12. O'Sullivan SE. An update on PPAR activation by cannabinoids. British Journal of Pharmacology. 2016; 173:1899–910. [PubMed: 27077495]
13. Li K, Fichna J, Schicho R, Saur D, Bashashati M, Mackie K, Li Y, Zimmer A, et al. A role for O-1602 and G protein-coupled receptor GPR55 in the control of colonic motility in mice. Neuropharmacology. 2013; 71:255–63. [PubMed: 23603203]
14. Duncan M, Thomas AD, Cluny NL, Patel A, Patel KD, Lutz B, Piomelli D, Alexander SP, et al. Distribution and function of monoacylglycerol lipase in the gastrointestinal tract. American Journal of Physiology. 2008; 295:G1255–65. [PubMed: 18948437]
15. Moody JS, Kozak KR, Ji C, Marnett LJ. Selective oxygenation of the endocannabinoid 2-arachidonylglycerol by leukocyte-type 12-lipoxygenase. Biochemistry. 2001; 40:861–6. [PubMed: 11170406]
16. Kozak KR, Crews BC, Morrow JD, Wang LH, Ma YH, Weinander R, Jakobsson PJ, Marnett LJ. Metabolism of the endocannabinoids, 2-arachidonylglycerol and anandamide, into prostaglandin, thromboxane, and prostacyclin glycerol esters and ethanolamides. The Journal of Biological Chemistry. 2002; 277:44877–85. [PubMed: 12244105]
17. Borrelli F, Izzo AA. Role of acylethanolamides in the gastrointestinal tract with special reference to food intake and energy balance. Best Practice & Research Clinical Endocrinology & Metabolism. 2009; 23:33–49. [PubMed: 19285259]

Europe PMC Funders Author Manuscripts

18. Coutts AA, Pertwee RG. Evidence that cannabinoid-induced inhibition of electrically evoked contractions of the myenteric plexus - longitudinal muscle preparation of guinea-pig small intestine can be modulated by Ca^{2+} and cAMP. Canadian Journal of Physiology and Pharmacology. 1998; 76:340–6. [PubMed: 9673798]
19. Pertwee RG. Cannabinoids and the gastrointestinal tract. Gut. 2001; 48:859–67. [PubMed: 11358910]
20. Chesher GB, Dahl CJ, Everingham M, Jackson DM, Marchant-Williams H, Starmer GA. The effect of cannabinoids on intestinal motility and their antinociceptive effect in mice. British Journal of Pharmacology. 1973; 49:588–94. [PubMed: 4788032]
21. Roth SH. Stereospecific presynaptic inhibitory effect of delta 9-tetrahydrocannabinol on cholinergic transmission in the myenteric plexus of the guinea pig. Canadian Journal of Physiology and Pharmacology. 1978; 56:968–75. [PubMed: 217512]
22. Izzo AA, Mascolo N, Borrelli F, Capasso F. Excitatory transmission to the circular muscle of the guinea-pig ileum: evidence for the involvement of cannabinoid CB1 receptors. British Journal of Pharmacology. 1998; 124:1363–8. [PubMed: 9723946]
23. Pertwee RG, Fernando SR, Nash JE, Coutts AA. Further evidence for the presence of cannabinoid CB1 receptors in guinea-pig small intestine. British Journal of Pharmacology. 1996; 118:2199–205. [PubMed: 8864562]
24. Pinto L, Izzo AA, Mascolo N, Capasso F, Cascio MG, Bisogno T, Di Marzo V, Hospodar-Scott K, et al. Endocannabinoids as physiological regulators of colonic propulsion in mice. Gastroenterology. 2002; 123:227–34. [PubMed: 12105851]
25. Mathison R, Ho W, Pittman QJ, Davison JS, Sharkey KA. Effects of cannabinoid receptor-2 activation on accelerated gastrointestinal transit in lipopolysaccharide-treated rats. British Journal of Pharmacology. 2004; 142:1247–54. [PubMed: 15249429]
26. Cluny NL, Keenan CM, Lutz B, Piomelli D, Sharkey KA. The identification of peroxisome proliferator-activated receptor alpha-independent effects of oleoylethanolamide on intestinal transit in mice. Neurogastroenterology and Motility. 2009; 21:420–9. [PubMed: 19140957]
27. Capasso R, Izzo AA, Fezza F, Pinto A, Capasso F, Mascolo N, Di Marzo V. Inhibitory effect of palmitoylethanolamide on gastrointestinal motility in mice. British Journal of Pharmacology. 2001; 134:945–50. [PubMed: 11682441]
28. Capasso R, Orlando P, Pagano E, Aveta T, Buono L, Borrelli F, Di Marzo V, Izzo AA. Palmitoylethanolamide normalizes intestinal motility in a model of post-inflammatory accelerated transit: involvement of CB(1) receptors and TRPV1 channels. British Journal of Pharmacology. 2014; 171:4026–37. [PubMed: 24818658]
29. Bashashati M, Nasser Y, Keenan C, Ho W, Piscitelli F, Nalli M, Mackie K, Storr M, et al. Inhibiting endocannabinoid biosynthesis: a novel approach to the treatment of constipation. British Journal of Pharmacology. 2015; 172:3099–111. [PubMed: 25684407]
30. Taschler U, Eichmann TO, Radner FPW, Grabner GF, Wolinski H, Storr M, Lass A, Schicho R, et al. Monoglyceride lipase-deficiency causes desensitization of intestinal cannabinoid receptor type 1 and increased colonic μ-opioid receptor sensitivity. British Journal of Pharmacology. 2015; 172:4419–29. [PubMed: 26075589]
31. Bashashati M, Storr MA, Nikas SP, Wood JT, Godlewski G, Liu J, Ho W, Keenan CM, et al. Inhibiting fatty acid amide hydrolase normalizes endotoxin-induced enhanced gastrointestinal motility in mice. British Journal of Pharmacology. 2012; 165:1556–71. [PubMed: 21883147]
32. Izzo AA, Pinto L, Borrelli F, Capasso R, Mascolo N, Capasso F. Central and peripheral cannabinoid modulation of gastrointestinal transit in physiological states or during the diarrhoea induced by croton oil. British Journal of Pharmacology. 2000; 129:1627–32. [PubMed: 10780967]
33. Vianna CR, Donato J, Rossi J, Scott M, Economides K, Gautron L, Pierpont S, Elias CF, et al. Cannabinoid receptor 1 in the vagus nerve is dispensable for body weight homeostasis but required for normal gastrointestinal motility. The Journal of Neuroscience. 2012; 32:10331–7. [PubMed: 22836266]
34. Croci T, Manara L, Aureggi G, Guagnini F, Rinaldi-Carmona M, Maffrand J, Fur G, Mukenge S, et al. In vitro functional evidence of neuronal cannabinoid CB 1 receptors in human ileum. British Journal of Pharmacology. 1998; 125:1393–5. [PubMed: 9884065]

Europe PMC Funders Author Manuscripts

35. Manara L, Croci T, Guagnini F, Rinaldi-Carmona M, Maffrand JP, Le Fur G, Mukenge S, Ferla G. Functional assessment of neuronal cannabinoid receptors in the muscular layers of human ileum and colon. Digestive and Liver Disease. 2002; 34:262–9. [PubMed: 12038810]
36. Guagnini F, Cogliati P, Mukenge S, Ferla G, Croci T. Tolerance to cannabinoid response on the myenteric plexus of guinea-pig ileum and human small intestinal strips. British Journal of Pharmacology. 2006; 148:1165–73. [PubMed: 16783406]
37. Guagnini F, Valenti M, Mukenge S, Matias I, Bianchetti A, Di Palo S, Ferla G, Di Marzo V, et al. Neural contractions in colonic strips from patients with diverticular disease: role of endocannabinoids and substance P. Gut. 2006; 55:946–53. [PubMed: 16423891]
38. Smid SD, Bjorklund CK, Svensson KM, Heigis S, Revesz A. The endocannabinoids anandamide and 2-arachidonoylglycerol inhibit cholinergic contractility in the human colon. European Journal of Pharmacology. 2007; 575:168–76. [PubMed: 17706636]
39. Izzo AA, Capasso F, Costagliola A, Bisogno T, Marsicano G, Ligresti A, Matias I, Capasso R, et al. An endogenous cannabinoid tone attenuates cholera toxin-induced fluid accumulation in mice. Gastroenterology. 2003; 125:765–74. [PubMed: 12949722]
40. Naidu PS, Booker L, Cravatt BF, Lichtman AH. Synergy between enzyme inhibitors of fatty acid amide hydrolase and cyclooxygenase in visceral nociception. The Journal of Pharmacology and Experimental Therapeutics. 2009; 329:48–56. [PubMed: 19118134]
41. Fernandez JR, Allison DB. R Rimonabant Sanofi-Synthélabo. Current Opinion in Investigational Drugs. 2004; 5:430–5. [PubMed: 15134285]
42. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends in Pharmacological Sciences. 2009; 30:515–27. [PubMed: 19729208]
43. de Filippis D, Iuvone T, d'amico A, Esposito G, Steardo L, Herman AG, Pelckmans PA, de Winter BY, et al. Effect of cannabidiol on sepsis-induced motility disturbances in mice: involvement of CB receptors and fatty acid amide hydrolase. Neurogastroenterology and Motility. 2008; 20:919–27. [PubMed: 18373655]
44. Capasso R, Borrelli F, Aviello G, Romano B, Scalisi C, Capasso F, Izzo AA. Cannabidiol, extracted from Cannabis sativa, selectively inhibits inflammatory hypermotility in mice. British Journal of Pharmacology. 2008; 154:1001–8. [PubMed: 18469842]
45. Van Sickle MD, Oland LD, Ho W, Hillard CJ, Mackie K, Davison JS, Sharkey KA. Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology. 2001; 121:767–74. [PubMed: 11606489]
46. Van Sickle MD, Duncan M, Kingsley PJ, Mouihate A, Urbani P, Mackie K, Stella N, Makriyannis A, et al. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science. 2005; 310:329–32. [PubMed: 16224028]
47. Suarez J, Romero-Zerbo SY, Rivera P, Bermudez-Silva FJ, Perez J, De Fonseca FR, Fernandez-Llebrez P. Endocannabinoid system in the adult rat circumventricular areas: an immunohistochemical study. The Journal of Comparative Neurology. 2010; 518:3065–85. [PubMed: 20533360]
48. Smith LA, Azariah F, Lavender VT, Stoner NS, Bettiol S. Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. The Cochrane Database of Systematic Reviews. 2015; doi: 10.1002/14651858.CD009464.pub2
49. Sticht MA, Long JZ, Rock EM, Limebeer CL, Mechoulam R, Cravatt BF, Parker LA. Inhibition of monoacylglycerol lipase attenuates vomiting in Suncus murinus and 2-arachidonoyl glycerol attenuates nausea in rats. British Journal of Pharmacology. 2012; 165:2425–35. [PubMed: 21470205]
50. Rock EM, Bolognini D, Limebeer CL, Cascio MG, Anavi-Goffer S, Fletcher PJ, Mechoulam R, Pertwee RG, et al. Cannabidiol, a non-psychotropic component of cannabis, attenuates vomiting and nausea-like behaviour via indirect agonism of 5-HT(1A) somatodendritic autoreceptors in the dorsal raphe nucleus. British Journal of Pharmacology. 2012; 165:2620–34. [PubMed: 21827451]
51. Sticht MA, Limebeer CL, Rafla BR, Parker LA. Intra-visceral insular cortex 2-arachidonoylglycerol, but not N-arachidonoylethanolamide, suppresses acute nausea-induced conditioned gaping in rats. Neuroscience. 2015; 286:338–44. [PubMed: 25499318]

Europe PMC Funders Author Manuscripts

52. Limebeer CL, Rock EM, Puvanenthirarajah N, Niphakis MJ, Cravatt BF, Parker LA. Elevation of 2-AG by monoacylglycerol lipase inhibition in the visceral insular cortex interferes with anticipatory nausea in a rat model. Behavioral Neuroscience. 2016; 130:261–6. [PubMed: 26974857]
53. Storr MA, Yuce B, Andrews CN, Sharkey KA. The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome. Neurogastroenterology and Motility. 2008; 20:857–68. [PubMed: 18710476]
54. Feng CC, Yan XJ, Chen X, Wang EM, Liu Q, Zhang LY, Chen J, Fang JY, et al. Vagal anandamide signaling via cannabinoid receptor 1 contributes to luminal 5-HT modulation of visceral nociception in rats. Pain. 2014; 155:1591–604. [PubMed: 24813296]
55. Fichna J, Wood JT, Papanastasiou M, Vadivel SK, Oprocha P, Salaga M, Sobczak M, Mokrowiecka A, et al. Endocannabinoid and cannabinoid-like fatty acid amide levels correlate with pain-related symptoms in patients with IBS-D and IBS-C: a pilot study. PloS ONE. 2013; 8:e85073. [PubMed: 24386448]
56. Izzo AA, Capasso R, Aviello G, Borrelli F, Romano B, Piscitelli F, Gallo L, Capasso F, et al. Inhibitory effect of cannabichromene, a major non-psychotropic cannabinoid extracted from Cannabis sativa, on inflammation-induced hypermotility in mice. British Journal of Pharmacology. 2012; 166:1444–60. [PubMed: 22300105]
57. Iwata Y, Ando K, Taniguchi K, Koba N, Sugiura A, Sudo M. Identification of a highly potent and selective CB2 agonist, RQ-00202730, for the treatment of irritable bowel syndrome. Bioorganic & Medicinal Chemistry Letters. 2015; 25:236–40. [PubMed: 25499880]
58. Fichna J, Salaga M, Stuart J, Saur D, Sobczak M, Zatorski H, Timmermans JP, Bradshaw HB, et al. Selective inhibition of FAAH produces antidiarrheal and antinociceptive effect mediated by endocannabinoids and cannabinoid-like fatty acid amides. Neurogastroenterology and Motility. 2014; 26:470–81. [PubMed: 24460851]
59. Sakin YS, Dogrul A, Ilkaya F, Seyrek M, Ulas UH, Gulsen M, Bagci S. The effect of FAAH, MAGL, and Dual FAAH/MAGL inhibition on inflammatory and colorectal distension-induced visceral pain models in Rodents. Neurogastroenterology and Motility. 2015; 27:936–44. [PubMed: 25869205]
60. Barbara G, Stanghellini V, De Giorgio R, Cremon C, Cottrell GS, Santini D, Pasquinelli G, Morselli-Labate AM, et al. Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology. 2004; 126:693–702. [PubMed: 14988823]
61. Facci L, Dal Toso R, Romanello S, Buriani A, Skaper SD, Leon A. Mast cells express a peripheral cannabinoid receptor with differential sensitivity to anandamide and palmitoylethanolamide. Proceedings of the National Academy of Sciences of the United States of America. 1995; 92:3376–80. [PubMed: 7724569]
62. Zheng G, Hong S, Hayes JM, Wiley JW. Chronic stress and peripheral pain: Evidence for distinct, region-specific changes in visceral and somatosensory pain regulatory pathways. Experimental Neurology. 2015; 273:301–11. [PubMed: 26408049]
63. Hong S, Zheng G, Wiley JW. Epigenetic regulation of genes that modulate chronic stress-induced visceral pain in the peripheral nervous system. Gastroenterology. 2015; 148:148–157.e7. [PubMed: 25263804]
64. Morena M, Patel S, Bains JS, Hill MN. Neurobiological Interactions Between Stress and the Endocannabinoid System. Neuropsychopharmacology. 2016; 41:80–102. [PubMed: 26068727]
65. Sharkey KA, Wiley JW. Getting Into the Weed: The Role of the Endocannabinoid System in the Brain-Gut Axis. Gastroenterology. 2016; doi: 10.1053/j.gastro.2016.04.015
66. Chiang KP, Gerber AL, Sipe JC, Cravatt BF. Reduced cellular expression and activity of the P129T mutant of human fatty acid amide hydrolase: evidence for a link between defects in the endocannabinoid system and problem drug use. Human Molecular Genetics. 2004; 13:2113–9. [PubMed: 15254019]
67. Camilleri M, Carlson P, McKinzie S, Grudell A, Busciglio I, Burton D, Baxter K, Ryks M, et al. Genetic variation in endocannabinoid metabolism, gastrointestinal motility, and sensation. American Journal of Physiology. 2008; 294:G13–9. [PubMed: 17962356]

Europe PMC Funders Author Manuscripts

68. Camilleri M, Kolar GJ, Vazquez-Roque MI, Carlson P, Burton DD, Zinsmeister AR. Cannabinoid receptor 1 gene and irritable bowel syndrome: phenotype and quantitative traits. American Journal of Physiology. 2013; 304:G553–60. [PubMed: 23306084]
69. Park JM, Choi MG, Cho YK, Lee IS, Kim SW, Choi KY, Chung IS. Cannabinoid receptor 1 gene polymorphism and irritable bowel syndrome in the Korean population: a hypothesis-generating study. Journal of Clinical Gastroenterology. 2011; 45:45–9. [PubMed: 20505532]
70. Jiang Y, Nie Y, Li Y, Zhang L. Association of cannabinoid type 1 receptor and fatty acid amide hydrolase genetic polymorphisms in Chinese patients with irritable bowel syndrome. Journal of Gastroenterology and Hepatology. 2014; 29:1186–91. [PubMed: 24444427]
71. Zhang SC, Wang WL, Su PJ, Jiang KL, Yuan ZW. Decreased enteric fatty acid amide hydrolase activity is associated with colonic inertia in slow transit constipation. Journal of Gastroenterology and Hepatology. 2014; 29:276–83. [PubMed: 23926887]
72. Esfandyari T, Camilleri M, Busciglio I, Burton D, Baxter K, Zinsmeister AR. Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. American Journal of Physiology. 2007; 293:G137–45. [PubMed: 17395895]
73. Klooker TK, Leliefeld KE, Van Den Wijngaard RM, Boeckxstaens GE. The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. Neurogastroenterology and Motility. 2011; 23:30–5, e2. [PubMed: 20718944]
74. Wong BS, Camilleri M, Busciglio I, Carlson P, Szarka LA, Burton D, Zinsmeister AR. Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. Gastroenterology. 2011; 141:1638–47.e1-7. [PubMed: 21803011]
75. Wong BS, Camilleri M, Eckert D, Carlson P, Ryks M, Burton D, Zinsmeister AR. Randomized pharmacodynamic and pharmacogenetic trial of dronabinol effects on colon transit in irritable bowel syndrome-diarrhea. Neurogastroenterology and Motility. 2012; 24:358–e169. [PubMed: 22288893]
76. Tack J, Piessevaux H, Coulie B, Caenepeel P, Janssens J. Role of impaired gastric accommodation to a meal in functional dyspepsia. Gastroenterology. 1998; 115:1346–52. [PubMed: 9834261]
77. Tack J, Caenepeel P, Fischler B, Piessevaux H, Janssens J. Symptoms associated with hypersensitivity to gastric distention in functional dyspepsia. Gastroenterology. 2001; 121:526–35. [PubMed: 11522735]
78. Ameloot K, Janssen P, Scarpellini E, Vos R, Boesmans W, Depoortere I, Vanden Berghe P, Tack J. Endocannabinoid control of gastric sensorimotor function in man. Alimentary Pharmacology & Therapeutics. 2010; 31:1123–31. [PubMed: 20146701]
79. Ly HG, Ceccarini J, Weltens N, Bormans G, Van Laere K, Tack J, Van Oudenhove L. Increased cerebral cannabinoid-1 receptor availability is a stable feature of functional dyspepsia: a [F]MK-9470 PET study. Psychotherapy and Psychosomatics. 2015; 84:149–58. [PubMed: 25833408]
80. Muccioli GG, Naslain D, Backhed F, Reigstad CS, Lambert DM, Delzenne NM, Cani PD. The endocannabinoid system links gut microbiota to adipogenesis. Molecular Systems Biology. 2010; 6:392. [PubMed: 20664638]
81. Cani PD, Plovier H, Hul MV, Geurts L, Delzenne NM, Druart C, Everard A. Endocannabinoids - at the crossroads between the gut microbiota and host metabolism. Nature Reviews Endocrinology. 2015; 12:133–43.
82. Jalanka-Tuovinen J, Salojarvi J, Salonen A, Immonen O, Garsed K, Kelly FM, Zaitoun A, Palva A, et al. Faecal microbiota composition and host-microbe cross-talk following gastroenteritis and in postinfectious irritable bowel syndrome. Gut. 2014; 63:1737–45. [PubMed: 24310267]
83. Rezaie A, Nikfar S, Abdollahi M. The place of antibiotics in management of irritable bowel syndrome: a systematic review and meta-analysis. Archives of Medical Science. 2010; 6:49–55. [PubMed: 22371720]

Europe PMC Funders Author Manuscripts

84. Rousseaux C, Thuru X, Gelot A, Barnich N, Neut C, Dubuquoy L, Dubuquoy C, Merour E, et al. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. Nature Medicine. 2007; 13:35–7.
85. Ringel-Kulka T, Goldsmith JR, Carroll IM, Barros SP, Palsson O, Jobin C, Ringel Y. Lactobacillus acidophilus NCFM affects colonic mucosal opioid receptor expression in patients with functional abdominal pain - a randomised clinical study. Alimentary Pharmacology & Therapeutics. 2014; 40:200–7. [PubMed: 24853043]
86. Aguilera M, Cerda-Cuellar M, Martinez V. Antibiotic-induced dysbiosis alters host-bacterial interactions and leads to colonic sensory and motor changes in mice. Gut Microbes. 2015; 6:10–23. [PubMed: 25531553]
87. Engel MA, Neurath MF. New pathophysiological insights and modern treatment of IBD. Journal of Gastroenterology. 2010; 45:571–83. [PubMed: 20213337]
88. Alhouayek M, Muccioli GG. The endocannabinoid system in inflammatory bowel diseases: From pathophysiology to therapeutic opportunity. Trends in Molecular Medicine. 2012; 18:615–25. [PubMed: 22917662]
89. Massa F, Marsicano G, Hermana H, Cannich A, Monory K, Cravatt BF, Ferri GL, Sibaev A, et al. The endogenous cannabinoid system protects against colonic inflammation. Journal of Clinical Investigation. 2004; 113:1202–9. [PubMed: 15085199]
90. Storr MA, Keenan CM, Zhang H, Patel KD, Makriyannis A, Sharkey KA. Activation of the cannabinoid 2 receptor (CB2) protects against experimental colitis. Inflammatory Bowel Diseases. 2009; 15:1678–85. [PubMed: 19408320]
91. D'Argenio G, Valenti M, Scaglione G, Cosenza V, Sorrentini I, Di Marzo V. Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation. The FASEB Journal. 2006; 20:568–70. [PubMed: 16403786]
92. Storr MA, Keenan CM, Emmerdinger D, Zhang H, Yüce B, Sibaev A, Massa F, Buckley NE, et al. Targeting endocannabinoid degradation protects against experimental colitis in mice: Involvement of CB1 and CB2 receptors. Journal of Molecular Medicine. 2008; 86:925–36. [PubMed: 18493729]
93. Alhouayek M, Lambert DM, Delzenne NM, Cani PD, Muccioli GG. Increasing endogenous 2-arachidonoylglycerol levels counteracts colitis and related systemic inflammation. The FASEB Journal. 2011; 25:2711–21. [PubMed: 21551239]
94. Salaga M, Mokrowiecka A, Zakrzewski PK, Cygankiewicz A, Leishman E, Sobczak M, Zatorski H, Malecka-Panas E, et al. Experimental colitis in mice is attenuated by changes in the levels of endocannabinoid metabolites induced by selective inhibition of fatty acid amide hydrolase (FAAH). Journal of Crohn's and Colitis. 2014; 8:998–1009.
95. Sasso O, Migliore M, Habrant D, Armirotti A, Albani C, Summa M, Moreno-Sanz G, Scarpelli R, et al. Multitarget fatty acid amide hydrolase/cyclooxygenase blockade suppresses intestinal inflammation and protects against nonsteroidal anti-inflammatory drug-dependent gastrointestinal damage. The FASEB Journal. 2015; 29:2616–27. [PubMed: 25757568]
96. Alhouayek M, Bottemanne P, Subramanian KV, Lambert DM, Makriyannis A, Cani PD, Muccioli GG. N-Acylethanolamine-hydrolyzing acid amidase inhibition increases colon N-palmitoylethanolamine levels and counteracts murine colitis. The FASEB Journal. 2015; 29:650–61. [PubMed: 25384424]
97. Borrelli F, Romano B, Petrosino S, Pagano E, Capasso R, Coppola D, Battista G, Orlando P, et al. Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent. British Journal of Pharmacology. 2015; 172:142–58. [PubMed: 25205418]
98. Esposito G, Capoccia E, Turco F, Palumbo I, Lu J, Steardo A, Cuomo R, Sarnelli G, et al. Palmitoylethanolamide improves colon inflammation through an enteric glia/toll like receptor 4-dependent PPAR-α activation. Gut. 2013; 63:1300–12. [PubMed: 24082036]
99. Tourteau A, Andrzejak V, Body-Malapel M, Lemaire L, Lemoine A, Mansouri R, Djouina M, Renault N, et al. 3-Carboxamido-5-aryl-isoxazoles as new CB2 agonists for the treatment of colitis. Bioorganic and Medicinal Chemistry. 2013; 21:5383–94. [PubMed: 23849204]
100. Engel MA, Kellermann CA, Burnat G, Hahn EG, Rau T, Konturek PC. Mice lacking cannabinoid CB1-, CB2-receptors or both receptors show increased susceptibility to trinitrobenzene sulfonic

Europe PMC Funders Author Manuscripts

acid (TNBS)-induced colitis. Journal of Physiology and Pharmacology. 2010; 61:89–97. [PubMed: 20228420]

101. Jamontt JM, Molleman A, Pertwee RG, Parsons ME. The effects of delta 9-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. British Journal of Pharmacology. 2010; 160:712–23. [PubMed: 20590574]
102. Borrelli F, Aviello G, Romano B, Orlando P, Capasso R, Maiello F, Guadagno F, Petrosino S, et al. Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. Journal of Molecular Medicine. 2009; 87:1111–21. [PubMed: 19690824]
103. de Filippis D, Esposito G, Cirillo C, Cipriano M, de Winter BY, Scuderi C, Sarnelli G, Cuomo R, et al. Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. PLoS ONE. 2011; 6:1–8.
104. Schicho R, Storr M. Topical and systemic cannabidiol improves trinitrobenzene sulfonic acid colitis in mice. Pharmacology. 2012; 89:149–55. [PubMed: 22414698]
105. Borrelli F, Fasolino I, Romano B, Capasso R, Maiello F, Coppola D, Orlando P, Battista G, et al. Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. Biochemical Pharmacology. 2013; 85:1306–16. [PubMed: 23415610]
106. Schicho R, Bashashati M, Bawa M, McHugh D, Saur D, Hu HM, Zimmer A, Lutz B, et al. The atypical cannabinoid O-1602 protects against experimental colitis and inhibits neutrophil recruitment. Inflammatory Bowel Diseases. 2011; 17:1651–64. [PubMed: 21744421]
107. Stančić A, Jandl K, Hasenöhrl C, Reichmann F, Marsche G, Schuligoi R, Heinemann A, Storr M, et al. The GPR55 antagonist CID16020046 protects against intestinal inflammation. Neurogastroenterology & Motility. 2015; 27:1432–45. [PubMed: 26227635]
108. Kargl J, Andersen L, Hasenoehrl C, Feuersinger D, Stancic A, Fauland A, Magnes C, El-Heliebi A, et al. GPR55 promotes migration and adhesion of colon cancer cells indicating a role in metastasis. British Journal of Pharmacology. 2016; 173:142–54. [PubMed: 26436760]
109. Alhamoruni A, Lee AC, Wright KL, Larvin M, O'Sullivan SE. Pharmacological effects of cannabinoids on the Caco-2 cell culture model of intestinal permeability. The Journal of Pharmacology and Experimental Therapeutics. 2010; 335:92–102. [PubMed: 20592049]
110. Harvey BS, Nicotra LL, Vu M, Smid SD. Cannabinoid CB2 receptor activation attenuates cytokine-evoked mucosal damage in a human colonic explant model without changing epithelial permeability. Cytokine. 2013; 63:209–17. [PubMed: 23706402]
111. Lal S, Prasad N, Ryan M, Tangri S, Silverberg MS, Gordon A, Steinhart H. Cannabis use amongst patients with inflammatory bowel disease. European Journal of Gastroenterology & Hepatology. 2011; 23:891–6. [PubMed: 21795981]
112. Ravikoff Allegretti J, Courtwright A, Lucci M, Korzenik JR, Levine J. Marijuana Use Patterns Among Patients with In fl ammatory Bowel Disease. Inflammatory Bowel Diseases. 2013; 19:2809–14. [PubMed: 24185313]
113. Naftali T, Lev LB, Yablekovitz D, Half E, Konikoff FM. Treatment of Crohn's disease with cannabis: an observational study. The Israel Medical Association Journal. 2011; 13:455–8. [PubMed: 21910367]
114. Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. Clinical Gastroenterology and Hepatology. 2013; 11:1276–1280.e1. [PubMed: 23648372]
115. Storr M, Devlin S, Kaplan GG, Panaccione R, Andrews CN. Cannabis use provides symptom relief in patients with inflammatory bowel disease but is associated with worse disease prognosis in patients with Crohn's disease. Inflammatory Bowel Diseases. 2014; 20:472–80. [PubMed: 24407485]
116. Ligresti A, Bisogno T, Matias I, De Petrocellis L, Cascio MG, Cosenza V, D'Argenio G, Scaglione G, et al. Possible endocannabinoid control of colorectal cancer growth. Gastroenterology. 2003; 125:677–87. [PubMed: 12949714]

117. Chen L, Chen H, Li Y, Li L, Qiu Y, Ren J. Endocannabinoid and ceramide levels are altered in patients with colorectal cancer. Oncology Reports. 2015; 34:447–54. [PubMed: 25975960]
118. Ye L, Zhang B, Seviour EG, Tao KX, Liu XH, Ling Y, Chen JY, Wang GB. Monoacylglycerol lipase (MAGL) knockdown inhibits tumor cells growth in colorectal cancer. Cancer Letters. 2011; 307:6–17. [PubMed: 21543155]
119. Wang D, Wang H, Ning W, Backlund MG, Dey SK, DuBois RN. Loss of cannabinoid receptor 1 accelerates intestinal tumor growth. Cancer Research. 2008; 68:6468–76. [PubMed: 18676872]
120. Cianchi F, Papucci L, Schiavone N, Lulli M, Magnelli L, Vinci MC, Messerini L, Manera C, et al. Cannabinoid receptor activation induces apoptosis through tumor necrosis factor alpha-mediated ceramide de novo synthesis in colon cancer cells. Clinical Cancer Research. 2008; 14:7691–700. [PubMed: 19047095]
121. Jung CK, Kang WK, Park JM, Ahn HJ, Kim SW, Oh S, Choi KY. Expression of the cannabinoid type I receptor and prognosis following surgery in colorectal cancer. Oncology Letters. 2013; 505:870–6.
122. Gustafsson SB, Palmqvist R, Henriksson ML, Dahlin AM, Edin S, Jacobsson SO, Öberg Å, Fowler CJ. High tumour cannabinoid CB 1 receptor immunoreactivity negatively impacts disease-specific survival in stage II microsatellite stable colorectal cancer. PLoS ONE. 2011; 6:e23003. [PubMed: 21901119]
123. Bedoya F, Rubio JC, Morales-Gutierrez C, Abad-Barahona A, Lora Pablos D, Meneu JC, Moreno-Gonzalez E, Salamanca ED, et al. Single nucleotide change in the cannabinoid receptor-1 (CNR1) gene in colorectal cancer outcome. Oncology. 2009; 76:435–41. [PubMed: 19420965]
124. Martínez-Martínez E, Gómez I, Martín P, Sánchez A, Román L, Tejerina E, Bonilla F, Merino AG, et al. Cannabinoids receptor type 2, CB2, expression correlates with human colon cancer progression and predicts patient survival. Oncoscience. 2015; 2:131–41. [PubMed: 25859556]
125. Izzo AA, Aviello G, Petrosino S, Orlando P, Marsicano G, Lutz B, Borrelli F, Capasso R, et al. Increased endocannabinoid levels reduce the development of precancerous lesions in the mouse colon. Journal of Molecular Medicine. 2008; 86:89–98. [PubMed: 17823781]
126. Aviello G, Romano B, Borrelli F, Capasso R, Gallo L, Piscitelli F, Di Marzo V, Izzo AA. Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer. Journal of Molecular Medicine. 2012; 90:925–34. [PubMed: 22231745]
127. Romano B, Borrelli F, Pagano E, Cascio MG, Pertwee RG, Izzo AA. Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. Phytomedicine. 2014; 21:631–9. [PubMed: 24373545]
128. Borrelli F, Pagano E, Romano B, Panzera S, Maiello F, Coppola D, De Petrocellis L, Buono L, et al. Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychotropic cannabinoid. Carcinogenesis. 2014; 35:2787–97. [PubMed: 25269802]
129. Kargl J, Haybaeck J, Stančić A, Andersen L, Marsche G, Heinemann A, Schicho R. O-1602, an atypical cannabinoid, inhibits tumor growth in colitis-associated colon cancer through multiple mechanisms. Journal of Molecular Medicine. 2013; 91:449–58. [PubMed: 22965195]
130. Santoro A, Pisanti S, Grimaldi C, Izzo AA, Borrelli F, Proto MC, Malfitano AM, Gazzerro P, et al. Rimonabant inhibits human colon cancer cell growth and reduces the formation of precancerous lesions in the mouse colon. International Journal of Cancer. 2009; 125:996–1003. [PubMed: 19479993]
131. Kogan NM, Schlesinger M, Peters M, Marincheva G, Beeri R, Mechoulam R. A cannabinoid anticancer quinone, HU-331, is more potent and less cardiotoxic than doxorubicin: a comparative in vivo study. The Journal of Pharmacology and Experimental Therapeutics. 2007; 322:646–53. [PubMed: 17478614]
132. Thapa D, Kang Y, Park P, Noh SK, Lee YR, Han SS, Ku SK, Jung Y, et al. Anti-tumor Activity of the Novel Hexahydrocannabinol Analog LYR-8 in Human Colorectal Tumor Xenograft Is Mediated through the Inhibition of Akt and Hypoxia-Inducible Factor-1α Activation. Biological and Pharmaceutical Bulletin. 2012; 35:924–32. [PubMed: 22687485]
133. Izzo, AA.; Muccioli, GG.; Ruggieri, MR.; Schicho, R. Endocannabinoids and the Digestive Tract and Bladder in Health and Disease. Endocannabinoids, Handbook of Experimental

Pharmacology 231. Pertwee, RG., editor. Springer International Publishing; Switzerland: 2015. p. 423-47.

134. Velasco G, Sánchez C, Guzmán M. Towards the use of cannabinoids as antitumour agents. Nature Reviews Cancer. 2012; 12:436–44.
135. Greenhough A, Patsos HA, Williams AC, Paraskeva C. The cannabinoid delta (9)-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. International Journal of Cancer. 2007; 121:2172–80. [PubMed: 17583570]
136. Pellerito O, Notaro A, Sabella S, De Blasio A, Vento R, Calvaruso G, Giuliano M. WIN induces apoptotic cell death in human colon cancer cells through a block of autophagic flux dependent on PPARgamma down-regulation. Apoptosis. 2014; 19:1029–42. [PubMed: 24696378]
137. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV, Keurentjes JC, Lang S, et al. Cannabinoids for Medical Use: A Systematic Review and Meta-analysis. Jama. 2015; 313:2456–73. [PubMed: 26103030]

Europe PMC Funders Author Manuscripts

Europe PMC Funders Author Manuscripts

Key points

- The endocannabinoid system (ECS) represents an important homeostatic entity of the gut that consists of cannabinoid receptors, their endogenous ligands (the “endocannabinoids”), and their synthesizing/degrading enzymes.
- A large number of studies have confirmed that the ECS is crucially involved in the control of motility, secretion and mucosal integrity of the gut and may even determine the course of intestinal inflammation and cancer. The ECS provides many drug targets for human gastrointestinal disorders, such as irritable bowel syndrome, inflammatory bowel disease and colon cancer.
- Conduction of clinical trials and translation into clinical application of cannabinoids are important future goals in this field.

Europe PMC Funders Author Manuscripts

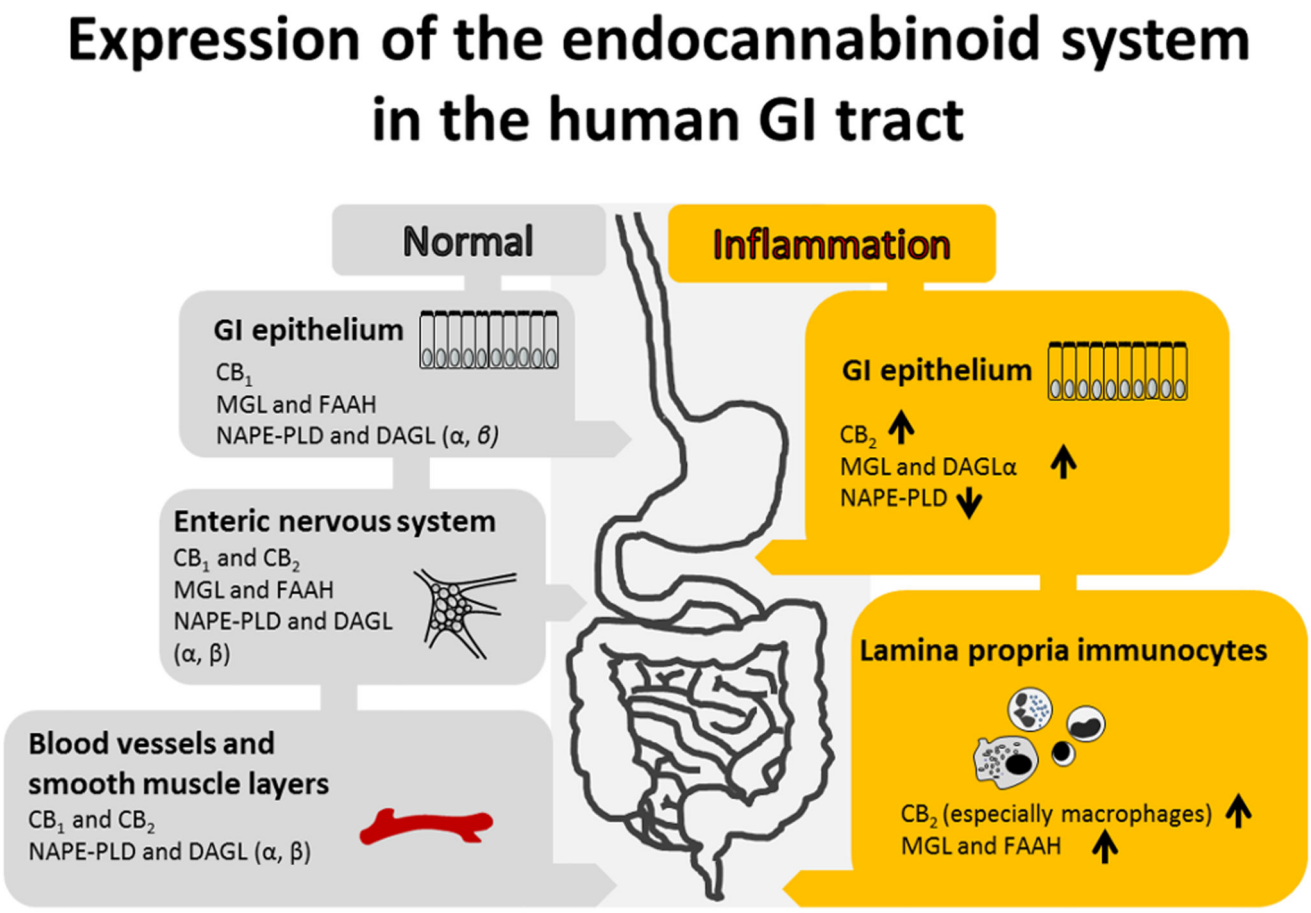

Fig. 1.

Expression of receptors and synthesizing/degrading enzymes of the endocannabinoid system (ECS) in the normal and acutely inflamed human gastrointestinal (GI) tract. Data were taken from Wright et al. (5) and Marquéz et al. (7). CB_1, CB_2, cannabinoid receptors 1 and 2; FAAH, fatty acid amide hydrolase; MGL, monoacylglycerol lipase; NAPE-PLD, N-acyl phosphatidylethanolamine phospholipase D; DAGL, diacylglycerol lipase.

Europe PMC Funders Author Manuscripts

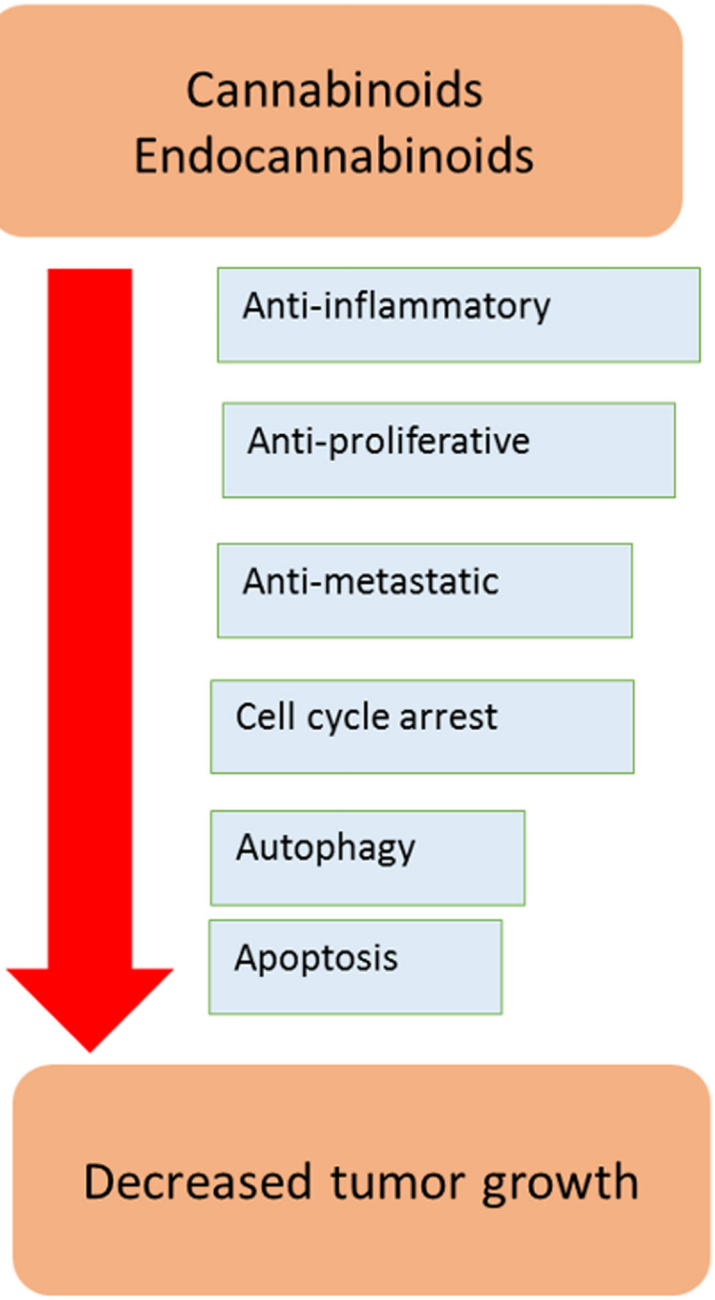

Fig. 2.

(Endo-) cannabinoids exert various anti-tumorigenic effects in colon cancer. For a more detailed description of molecular mechanisms in which cannabinoids and endocannabinoids could play a role, the reader is referred to Velasco et al. (134).