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REVIEW ARTICLE

The role of the endocannabinoid system in the pathophysiology and treatment of irritable bowel syndrome

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Abstract *Irritable bowel syndrome (IBS) is a spectrum of disorders characterized by abdominal discomfort and pain, associated with altered bowel habits. Though gut motility, secretion and sensation may be altered in patients with IBS, the pathophysiology of this condition remains to be fully understood. The endocannabinoid system is involved in the regulation of numerous gastrointestinal functions including motility, sensation and secretion under both physiological and pathophysiological conditions. Activation of cannabinoid (CB)$_1$ and CB$_2$ receptors under various circumstances reduces motility, limits secretion and decreases hypersensitivity in the gut. Drugs that alter the levels of endocannabinoids in the gut also reduce motility and attenuate inflammation. In this review, we discuss the role of the endocannabinoid system in gastrointestinal physiology. We go on to consider the involvement of the endocannabinoid system in the context of symptoms associated with IBS and a possible role of this system in the pathophysiology and treatment of IBS.*

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Abbreviations: 2-AG, 2-arachidonyl glyercol; CB$_1$, cannabinoid-1; CB$_2$, cannabinoid-2; ChAT, choline-acetyltransferase; EMT, endocannabinoid membrane transporter; FAAH, fatty acid amide hydrolase; HAPCs, high-amplitude propagated contractions; IBS, irritable bowel syndrome; MAP kinase, mitogen-activated protein kinase; MAGL, monoacylglycerol lipase; SNP, single nucleotide polymorphism; THC, tetrahydrocannabinol; TNBS, trinitrobenzene sulphonic acid; TRPV1, transient receptor potential vanilloid receptor 1.

INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder characterized by abdominal discomfort, pain and altered bowel habits.[1,2] The most recent diagnostic criteria, the Rome III criteria, define the syndrome as recurrent abdominal pain or discomfort at least 3 days per month over 3 months, which is associated with two or more of the following characteristics: (i) improvement with defecation, (ii) onset associated with a change in stool frequency and (iii) onset associated with a change in stool form. Symptom patterns can be divided into diarrhoea predominant (D-IBS), constipation predominant (C-IBS) and a mixed pattern (M-IBS).[2] The disorder is incredibly common, with 10–20% of adults throughout the developed world having symptoms consistent

with IBS.[3] Standard clinical investigations such as endoscopy or blood tests generally show no abnormalities, and thus diagnosis is made based on clinical history and patient symptoms.[4]

The pathophysiology of IBS is complex. The current understanding incorporates biological and psychosocial factors as playing a role in the onset and propagation of symptoms, and is known as the biopsychosocial model.[4] Various abnormalities have been found in different groups of IBS patients, including altered gut motility, visceral hypersensitivity, disturbances of brain–gut interactions and central processing of visceral afferent information. In addition, a host of other autonomic, hormonal, psychological, environmental and genetic factors probably contribute to IBS.[4] It is unlikely that a single unifying hypothesis will explain the pathophysiology in all IBS patients; it is thus viewed as an interaction of a variable number of these factors for any given patient.

THE ENDOCANNABINOID SYSTEM IN THE GASTROINTESTINAL TRACT

Cannabinoid receptors

In 1990, the first cannabinoid receptor was cloned by Matsuda *et al.* and named CB_1.[5] Subsequently, a second cannabinoid receptor (CB_2) was identified in 1992, sharing a 48% homology with the CB_1 receptor.[6] The discovery of the endogenous ligands for these receptors provided the basis for the establishment of the 'endocannabinoid system', a term first coined by Di Marzo and Fontana in 1995.[7]

Since then an additional splice variant of the CB_1 receptor (CB_{1A}) has been reported, but its actual function is not yet clear.[8] Furthermore, several other putative CB receptors have been identified, with GPR55 and GPR119 being the most promising CB receptor candidates.[9] The established CB receptors show a distinct distribution in the gastrointestinal tract with CB_1 and recently, CB_2 receptors, being described in the enteric nervous system.[10–12] CB_1 receptors are also localized on epithelial cells[13] and CB_2 receptors are present on immune cells.[6,13] Both receptors are coupled negatively through G_i/G_o-type G proteins to adenylate cyclase and positively to mitogen-activated protein kinase (MAP kinase),[6] but little is known regarding the exact cellular mechanisms involved after their activation in the gastrointestinal tract. Currently, it is not known where the putative novel CB receptors are localized in the gastrointestinal tract.

Immunohistochemistry and functional studies have shown that CB_1 receptors are distributed on intrinsic and extrinsic nerves of the gastrointestinal tract. The intrinsic neurons are located in the myenteric and submucosal plexuses of the enteric nervous system. These plexuses consist of motor neurons, interneurons and primary afferent neurons, and CB_1 receptors appear to be localized on all of these functional classes. Using immunohistochemical staining and co-localization analysis, CB receptors were found on different neuronal subtypes of the enteric nervous system. Double-labelling of CB_1 immunoreactivity with choline-acetyltransferase (ChAT), calretinin and substance P suggests that CB_1 is present on excitatory motor neurons,[10,14] some classes of interneurons and enteric sensory neurons. In addition, the presence of CB_1 receptors on interneurons has been suggested by functional studies.[15] Co-localization with calbindin, an immunohistochemical marker for intrinsic primary afferent neurons, further supports the possibility of CB_1 expression in these enteric sensory neurons.[10] CB_1 receptor is not found on neurons containing nitric oxide synthase.[10,14] CB_2 receptor mRNA was shown in the oesophagus, stomach and ileum of rats and with Western blotting CB_2 receptor protein expression was shown in the rat ileum.[11,12] Recently, using immunohistochemistry, CB_2 receptors were localized on most neurons of the enteric nervous system of the rat ileum,[11] though again it is largely absent from neurons containing nitric oxide synthase.

Endogenous cannabinoid receptor ligands – endocannabinoids

Several endocannabinoids have been reported with affinities to both CB_1 and CB_2 receptors.[6] The first endocannabinoid isolated in the gastrointestinal tract was anandamide, which is not only an endocannabinoid but also an endovanilloid and activates CB_1, CB_2 and TRPV1 (transient receptor potential vanilloid 1) receptors.[6,16,17] The second endocannabinoid isolated from the gut was 2-arachidonyl glycerol (2-AG).[18] Pharmacological studies have demonstrated effects of other putative endocannabinoids on gastrointestinal tissues (for example, noladin ether, *N*-arachidonoyldopamine and virodhamine)[19–21] but evidence that these molecules are present in the gastrointestinal tract is currently lacking.

Endocannabinoid synthesis and degradation

Several components of endocannabinoid metabolism have been characterized. Endocannabinoids like anandamide and 2-AG are synthesized on demand from fatty acid precursors by specific phospholipases

and are then released to the extracellular space.[22–25] The actions of endocannabinoids are terminated intracellularly where enzymatic degradation takes place.[26] Endocannabinoids freely diffuse from the extracellular space through the plasma membrane and additionally an endocannabinoid membrane transporter (EMT) is thought to carry endocannabinoids into the cell for degradation, but it has not yet been cloned and its existence is still controversial.[27] However, drugs that are proposed to be EMT inhibitors have been synthesized.[24] Anandamide breakdown is catalyzed by the enzyme fatty acid amide hydrolase (FAAH), a membrane bound protein,[22,26,28] whereas 2-AG is primarily degraded by the enzyme monoacylglycerol lipase (MAGL). Fatty acid amide hydrolase is present in the gastrointestinal tract, and in mice FAAH mRNA expression is the highest in the duodenum and the distal colon.[29] Monoacylglycerol lipase mRNA and protein was recently shown to be present in the enteric nervous system.[30]

The exact source of endocannabinoids and the specific stimulus for endocannabinoid release in the gut is still unknown. Furthermore, it is unclear whether there is regulation of the expression of endocannabinoid degrading enzymes in the gut, though there are alterations in the levels of endocannabinoids in states of inflammation and in celiac disease.[31,32] Local release of endocannabinoids seems likely and *in vitro* in stimulated cell cultures of dorsal root ganglia anandamide can be released,[33] suggesting that primary afferents can release the molecules. Whether release into the extracellular space involves an active transport mechanism or uncontrolled passive diffusion after their synthesis is unknown. It seems likely that the enteric nervous system is an important source of endocannabinoids, but currently, no information on endocannabinoid release in the gut is available. Macrophages, platelets and epithelia could also be a source of endocannabinoids, especially in states of inflammation.[34,35] Therefore, the peripheral actions of endocannabinoids in the gastrointestinal tract could also be due to a contribution from circulating sources. An overview of the endocannabinoid system is shown in Fig. 1.

IRRITABLE BOWEL SYNDROME, MOTILITY AND ENDOCANNABINOIDS

Studies assessing gut motility in IBS have recently been reviewed.[4,36] Focusing specifically on the colon and rectum, some findings have been shown fairly consistently. Colonic transit[37] and high-amplitude propagated contractions (HAPCs)[38,39] appear to be increased in D-IBS, whereas transit may be slower with less HAPCs in C-IBS.[40,41] Exaggerated phasic colonic contractile responses to a meal have also been shown consistently in IBS patients.[38,39,42] It is unclear, however, whether these findings explain the symptoms, the

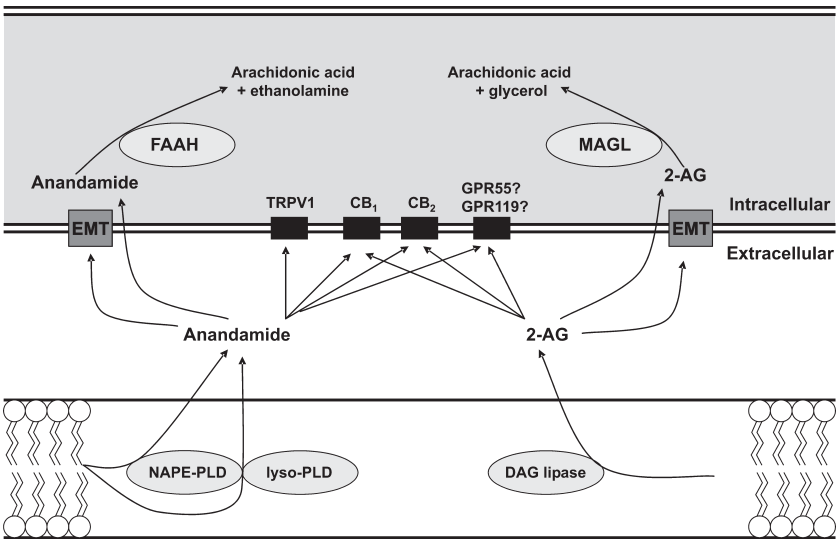

Figure 1 The endocannabinoid system. Biosynthesis of endocannabinoids involves multiple enzymatic steps where endocannabinoids are synthesized from membrane phospholipids. The final step of the biosynthetic pathways involve the enzymes *N*-acyl-phosphatidylethanolamine (NAPE-PLD) and lyso-PLD for anandamide and diacylglycerol-lipase (DAG-lipase) for 2-arachidonylglycerol (2-AG). After diffusion to the extracellular space the endocannabinoids act on cannabinoid (CB_1), CB_2, transient receptor potential vanilloid 1 (TRPV1) and possibly on G-protein-coupled receptors (GPR) 55 and 119. Their action is terminated by uptake in the intracellular space by passive diffusion or a specific endocannabinoid membrane transporter (EMT) and enzymatic degradation by the enzymes fatty acid amide hydrolase (FAAH) and monoacylglycerol-lipase (MAGL).

patients with IBS experience. Considering that shifts in bowel habit are a feature of IBS, even between the extremes of stool consistency (for example, from constipation-predominance to diarrhoea–predominance),[43] it remains questionable whether transit and HAPC frequency alone account for these symptoms.[44]

A substantial amount of evidence shows that stimulation of CB_1 receptors slows motility throughout the gut, including the colon.[45–47] This is in contrast to CB_2 receptors, which do not appear to have a significant effect on gut motility under physiological circumstances, but potentially regulate motility in pathophysiological states.[11,18] CB_1 receptors are located prejunctionally on cholinergic nerves and inhibit acetylcholine release when activated. These findings have been reviewed in detail elsewhere.[45–47] *In vitro* studies in multiple species have shown that CB_1 receptor agonists inhibit contraction of muscle throughout the gastrointestinal tract. These effects are largely reversed by CB_1 receptor selective antagonists demonstrating the involvement of CB_1 receptors.[12,48–50] Similar findings were reported in human colonic tissue *in vitro*, suggesting that the endocannabinoid mechanisms in control of motility, which have been characterized in laboratory animals are similar in humans.[51–54]

The physiological involvement of the endocannabinoid system in the regulation of gastrointestinal motility was demonstrated *in vitro* and *in vivo*. Treatment of animals with CB_1 receptor antagonists resulted in increased motility, suggesting that gastrointestinal motility is under a tonic suppression by the endocannabinoid system.[15,55,56] In addition, studies using FAAH blockers or EMT inhibitors *in vivo* demonstrate a slowing of gastrointestinal motility.[29] These results further support the concept that the endocannabinoid system is tonically active under physiological conditions, once again stressing the important role of the endocannabinoid system in the regulation of motility.[29]

In vivo studies in rodents have shown inhibition of intestinal and colonic transit by CB_1 receptor agonists[57] and increased transit with the CB_1 receptor antagonist rimonabant.[58] In humans, the CB_1/CB_2 receptor agonist dronabinol [synthetic Δ^9-tetrahydrocannabinol (THC)] taken orally decreased postprandial colonic tone and increased compliance[59] but did not affect colonic transit.[60] Clinical trials with selective CB receptor agonists and/or antagonists are required to translate present knowledge from laboratory animals to humans.

The only large clinical trials with CB_1 receptor antagonists were performed in patients with metabolic disorders and obesity.[61,62] From these trials, it seems very likely that gastrointestinal motility in humans is under control of the endogenous cannabinoid system. The clinical trials using the CB_1 antagonists rimonabant and taranabant showed that diarrhoea and other gastrointestinal motor side effects like nausea and vomiting being frequently observed, though often transient.[61–63]

It thus appears that the effects of the cannabinoid system on motility in humans are similar to those in rodents. Cannabinoid agents (agonists or antagonists) have not been studied clinically in IBS patients, but this may be worthwhile. From a motility standpoint, cannabinoid agonists might be helpful in conditions associated with diarrhoea and cannabinoid antagonists might be helpful in conditions associated with constipation. However, it has to be taken into account that the use of CB_1 receptor agonists is limited by the central psychotropic side effects. It is also important to point out that CB_1 receptor antagonists such as rimonabant and taranabant, are also accompanied by central side effects, since in clinical trials with rimonabant and taranabant, anxiety and a risk of depressive symptoms were noted.[62,63] CB_2 receptor-mediated effects on motility are less well characterized but there is strong evidence that these drugs alter motility in pathophysiological conditions and should therefore be considered in IBS. It remains speculative whether peripherally restricted compounds like Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl)methanone are devoid of the central side effects and would therefore be suitable for use in humans.[64] Another option is drugs targeting endocannabinoid degradation like FAAH blockers and EMT inhibitors, which increase endogenous cannabinoid levels and seem to be largely free of central side effects. Drugs targeting endocannabinoid degradation are presently developed by different companies (see below). Furthermore, drugs targeting endocannabinoid generation could be useful but no such drugs have yet been described.

THE ENDOCANNABINOID SYSTEM IN VISCERAL HYPERSENSITIVITY AND PAIN

Abdominal pain is a common symptom of gastrointestinal diseases and is influenced by both peripheral and central mechanisms of pain perception and transmission. In functional gastrointestinal disorders, like IBS, there is strong evidence for peripheral and central neural structures being involved in mechanisms resulting in visceral hypersensitivity.[65–67] Acute or chronic inflammation has been suggested as a possible trigger for the development of IBS.[66,68,69] Cannabinoids have well-described analgesic effects in various animal models of acute and chronic pain.[70] The finding that components of the endocannabinoid system are involved in pain transmission and modulation makes the endocannabi-

noid system a promising target for therapies in disorders where visceral pain is prominent.[71]

Animal models of visceral pain recently provided evidence that the endocannabinoid system is involved in visceral sensation.[72,73] Both CB_1 and CB_2 receptor agonists reduce the visceromotor responses in rodents to graded colorectal distention.[73] Two publications independently showed that after inducing hyperalgaesia by rectal instillation of trinitrobenzene sulphonic acid (TNBS), lower doses of CB receptor agonists were needed to reduce sensitivity to colorectal distention.[72,73] This clearly indicates that during hyperalgesic states the endocannabinoid system is more sensitive, and suggests that in these states, like IBS, patients might be more sensitive to cannabinoid treatment.

Whether the endocannabinoid system is involved in the pathophysiology of IBS is unknown, but as the CB_1 receptor antagonist rimonabant increases hypersensitivity in rectal distention models, a role of the CB_1 receptor in the physiological regulation of visceral sensitivity is conceivable.[73] In contrast, the CB_2 receptor antagonist SR 144528 did not alter thresholds to colorectal distention in these models making a physiological involvement of the CB_2 receptor in the regulation of visceral hypersensitivity unlikely.[72,73]

The location of the CB receptors involved in the regulation of visceral hypersensitivity remains unclear, but for the CB_2 receptor a peripheral site seems likely, as CB_2 receptor activation reduces mesenteric afferent activity in response to bradykinin in mice *in vivo*, whereas such influences of CB_1 receptors on mesenteric afferent neuronal activity was not shown.[74]

Whether these findings can be translated into human disease remains to be shown. In healthy volunteers, dronabinol slightly increased sensory ratings for pain during phasic colonic distention, whereas thresholds for gas sensation were unchanged.[59] Interestingly, this occurred despite an increase in colonic compliance and decreased postprandial colonic tone. Further research is needed to clarify whether the endocannabinoid system is involved in the origination, perpetuation, or resolution of painful symptoms in patients with IBS and whether drugs acting at CB receptors or other elements of the endocannabinoid system reduce visceral hypersensitivity in patients with IBS.

It is important to keep in mind that endocannabinoids, like anandamide, also act as agonists at other receptors, including the TRPV1 receptor and other members of the TRP family of receptors. It is worth mentioning that involvement of the TRPV1 receptors in visceral hypersensitivity was reported using animal models of colorectal distension.[75] TRPV1 immunoreactivity was reported in dorsal root ganglia and in the gastrointestinal tract,[76] which is consistent with them having a role in gastrointestinal pain transmission. A recent publication identified that cannabinoids exert analgesic effects in postinflammatory pain models by activation of Transient Receptor Potential A1 receptors, once again highlighting the overlap of the endocannabinoid system and the endovanilloid system.[77]

Evidence also exists for a role of TRPV1 in visceral hypersensitivity in humans. Immunohistochemical studies in patients with rectal hypersensitivity showed increased TRPV1 staining suggesting an activated endovanilloid system[78] and a recent study confirmed the increase of TRPV1 positive nerve fibres in colonic biopsies of patients with IBS and abdominal pain.[79]

It is presently unknown whether raising endocannabinoid levels with FAAH blockers or combination treatment with agonists at CB_1, CB_2 and TRPV1 receptors show additive or synergistic effects on rectal pain sensation. This needs to be addressed in future animal models, since if so, combination therapy could help to limit central side effects. Additionally, it has not been investigated whether compounds like anandamide which acts on both CB_1 and TRPV1 receptors as an agonist, results in analgesic or algesic effects, as these effects would be elicited upon activation of either the CB_1 or the TRPV1 receptor and the level of expression of these receptors under pathophysiological conditions may influence the overall dominant response.

ENDOCANNABINOIDS AND THE ENDOCANNABINOID SYSTEM IN SECRETION

Fluid secretion into the intestinal lumen contributes to digestive processes and the passage of gut contents. A role of intestinal secretion in the pathophysiology of IBS is still controversial.[80] In the distal ileum and colon, excess fluid is absorbed limiting water loss in the stool and contributing to normal bowel movements. Any failure to absorb water or excessive secretion leads to diarrhoea. The control of secretion and absorption is tightly regulated by neural, humoral and paracrine factors. Under physiological conditions cannabinoids inhibit intestinal secretion *in vitro* when administered exogenously.[81] It has been shown that CB_1 receptors are present in the submucosal plexus where they act to limit cholinergic nerve-mediated secretion. Interestingly, in the guinea pig it was reported that CB_1 receptors, present on capsaicin-sensitive extrinsic primary afferents, mediated the inhibitory actions of exogenous agonists on secretion assessed in isolated ileal preparations.[82] Rats given rimonabant had higher fecal water content than

animals treated with vehicle.[58] Similarly, they also had higher levels of fluid accumulation in the small intestine. Under pathophysiological conditions, rimonanbant enhanced cholera toxin-induced fluid accumulation, whereas the CB_2 receptor antagonist SR144528 had no effect.[83] Conversely, the EMT inhibitor VDM11 reduced cholera toxin-induced fluid secretion, suggesting the endocannabinoids released in the wall of the gut normally limit the degree of secretion through activation of CB_1 receptors. In both these studies, the authors provided evidence that these actions were mediated peripherally, presumably at the level of the enteric nervous system.

The role of endocannabinoids in IBS-related secretory abnormalities or in the control of secretion in animal models of IBS has not been evaluated. Given the potential role of the cannabinoid system, notably CB_1 receptors, in regulating epithelial function in the gut,[84] these studies are warranted.

ENDOCANNABINOIDS AND THE ENDOCANNABINOID SYSTEM IN INFLAMMATION

Postinfectious IBS is one accepted subgroup in IBS accounting for between 4% and 30% of IBS patients.[69,85,86] A recent meta-analysis revealed that the odds of developing IBS are increased sixfold after acute gastrointestinal infection[85] but some recent studies suggest lower odds ratios.[87,88] In addition, morphological studies indicate that inflammatory cell infiltration of the intestinal wall can be observed in many patients with IBS.[89,90] In this context, the potential role of the endocannabinoid system in the pathophysiology of intestinal inflammation is of interest, with the perspective that targeting the endocannabinoid system might protect against intestinal inflammation. Most of the information discussed here comes from animal models mimicking features of inflammatory bowel disease (IBD) thus the results must be interpreted cautiously with respect to IBS.

Gastrointestinal anti-inflammatory mechanisms of cannabinoids are presently characterized only in animal models. Activation of the endocannabinoid system has been described in a model of acute inflammation. The administration of croton oil in mice, increased the expression of CB_1 receptors and the CB_1/CB_2 receptor agonist WIN 55,212-2 was more effective in slowing motility in inflamed animals compared to control.[91] This strongly suggests a physiological protective role of the endocannabinoid system in inflammation-associated motility alterations, but there is little information on the involvement of possible downstream mechanisms.[55,91] Treatment with exogenous cannabinoids attenuates inflammation in experimental models of colitis and treatment with selective agonists in receptor deficient mice ($CB_1^{-/-}$ and $CB_2^{-/-}$), show that both CB_1 and CB_2 receptors are involved in the protective mechanisms against colitis that are activated by exogenous cannabinoids,[31,92–94] a finding that is further supported by CB_1 receptor upregulation and increased levels of anandamide during colitis.[31,93] Anandamide is an endovanilloid and, consistent with this, the TRPV1 receptor is also involved in protective mechanisms.[95–97] The involvement of not only CB_1 but also CB_2 receptors in protective mechanisms against TNBS colitis highlights the importance of the entire endocannabinoid system in colitis. Interestingly, the protective actions of CB_2 receptor agonists were also observed in the oil of mustard model of colitis, which has a substantial neurogenic component,[92] suggesting the involvement of neuronal mechanisms in the protective actions. This highlights the potential for cannabinoids to act on various elements in the gut wall to regulate inflammatory processes.[92,98–101]

Aside from direct receptor activation, there is evidence that manipulation of endocannabinoid degradation elicits beneficial effects. Attenuation of endocannabinoid degradation can be accomplished by blocking endocannabinoid membrane transport and/or by inhibiting FAAH (genetically); both potentially lead to elevated levels of endocannabinoids and have beneficial actions in colitis.[31,94]

The mechanisms of cannabinoid-mediated protection in colitis are less well described, and presently increased epithelial wound healing has been suggested,[13] but increased epithelial wound healing does not explain all the actions of cannabinoids. In other models of inflammation, cannabinoids have been shown to reduce inflammation by reducing chemotaxis of activated T cells, attenuating proinflammatory cytokine production and by shifting the balance of T-cell activation from Th1 to Th2 type responses,[102–104] but such mechanisms have not been shown for the gastrointestinal tract or patients with IBS. Many of these findings are attributed to CB_2 receptor activation, and the role of CB_1 receptors has either not been shown or not been investigated.

In summary, the endocannabinoid system is physiologically involved in mechanisms of protection against intestinal inflammation and several studies suggest activation of the endocannabinoid system during inflammation. Agents affecting the cannabinoid system have not yet been studied for their anti-inflammatory properties in humans due to the incomplete characterization of the anti-inflammatory

mechanisms and side effects of CB receptor agonists. However, manipulation of this system with pharmacological approaches offers the potential to reduce inflammation without utilizing CB receptor agonists. The potential role of the endocannabinoid system in the pathophysiology of postinflammatory IBS has yet to be determined as well as the possible treatment of these states with cannabinoids.

THE ENDOCANNABINOID SYSTEM AND GUT MICROBIOTA

The gut microflora is comprised numerous bacterial species that reside in the lumen along the length of the gut. Certain probiotics have been reported to alter abdominal symptoms associated with IBS in humans[105] and reduce visceral hypersensitivity in rats and mice.[106,107] In a recent study, a link has been made between gut microflora and the expression of CB_2 receptors.[108] In cell culture experiments, *Lactobacillus acidophilus* increased CB_2 mRNA expression in epithelial cells compared to untreated cells or cells treated with other bacteria. Enhanced CB_2 (and mu opioid) receptor expression was upregulated after chronic treatment (15 days) with *Lactobacillus acidophilus in vivo*. Interestingly, the CB_2 receptor antagonist AM630 reduced the *Lactobacillus acidophilus*-induced reduction in rectal sensitivity, suggesting that contact of *Lactobacillus acidophilus* with epithelial cells is able to induce CB_2 expression and contribute to the restoration of the normal perception of visceral sensation. It is presently unknown whether the normal gut microbiota alters CB_2 expression and thus visceral sensitivity and whether acute or chronic alterations of the gut microbiota, as they occur in patients with postinfectious IBS results in ongoing changes of CB_2 expression and are involved in the pathophysiology of IBS. There is presently no information available whether bacteria cause alterations of CB_1, FAAH or MAGL expression and whether such alterations are involved in the regulation of visceral sensitivity.

Though CB receptor activation is known to be involved in numerous immune mechanisms, no further information is available whether the endocannabinoid system is involved in regulation of gut microbiota or to the extent gut microbiota alters the activity of the endocannabinoid system. The above mentioned study reveals such interactions and concomitant functional alterations, but further studies are needed to establish the potential pathophysiological role of the endocannabinoid system in patients with postinfectious IBS or functional alterations associated with small intestinal bacterial overgrowth.

CANNABINOID DRUG DEVELOPMENT

Dronabinol (Marinol®; Solvay Pharmaceuticals, Bruxelles, Belgium), an agonist of both CB_1 and CB_2 receptors, is marketed as an appetite stimulant and anti-emetic in many countries. The CB_1 receptor antagonist Rimonanbant (Acomplia®; Sanofi-Aventis, Paris, France) is available to treat obese patients in some countries, notably in Europe. In Canada, the oromucosal spray containing THC and cannabidiol is marketed under the brand name Sativex® (GW Pharmaceuticals, Salisbury, UK) for the alleviation of pain and spasticity in multiple sclerosis patients and is expected to be approved in other countries soon.

Cannabinoid research is a hot topic not only amongst academic institutions but also in industry, including global pharmaceutical companies such as AstraZeneca, Bayer AG, Bristol-Myers Squibb, Eli Lilly, Indevus Pharmaceuticals, Merck & Co, Novartis, Pharmos, Pfizer, Sanofi-Aventis, Schering, SmithKline Beecham, GW Pharmaceuticals and Solvay Pharmaceuticals. A patent search (Google patent search) shows that numerous pharmacological inventions in this field were filed in recent years with gastrointestinal indications forming part of nearly all of them. Some of the inventions are focused on gastrointestinal uses, with agents affecting gastrointestinal motility, gastrointestinal pain and gastrointestinal inflammation indicating the high impact industry attributes to targeting the endocannabinoid system in functional gastrointestinal disorders. These pharmacological inventions include novel receptor-selective agonists and antagonists with higher selectivity and higher potency and also drugs such as neutral antagonists (devoid of inverse agonist properties), agonists specific for peripheral receptors or agonists with limited blood–brain barrier penetration. Other interesting compounds include drugs with CB_2 agonistic/CB_1 antagonistic properties, novel non-psychotropic cannabinoids and cannabinoids with alterations in absorption characteristics and improved tissue penetration. In addition, patents have been filed for drugs acting on endocannabinoid degradation such as novel FAAH inhibitors and EMT blockers. Presently, no information is available whether these drugs are already tested in Phase 1 or Phase 2 clinical trials.

THE ENDOCANNABINOID SYSTEM IN THE GENETICS OF IBS

Though the pathophysiology of IBS remains uncertain, hereditary factors are likely to have a role.[109] Studying single nucleotide polymorphism (SNP) phenotype associations is one way to study hereditary factors.

Recently, an SNP in the FAAH gene (C385A), which was shown to result in enhanced sensitivity to proteolytic degradation of FAAH,[110] was shown to be associated with changes in colonic transit time and with distinct phenotypes of IBS.[111] Though unproven, it may be hypothesized that in subjects homozygous for the FAAH SNP, endocannabinoid metabolism is impaired and degradation of endocannabinoids is reduced, which might result in increased local endocannabinoid levels and subsequently altered gastrointestinal function. In this study, the FAAH SNP was significantly associated with accelerated colonic transit in patients with D-IBS. However, in other patient groups (C-IBS; M-IBS, functional dyspepsia) no associations with colonic transit, gastric emptying or rectal sensation thresholds in rectal barostat investigations were found. Interestingly, further associations of the FAAH SNP were found for D-IBS and M-IBS phenotype, but not with C-IBS or functional dyspepsia phenotype. The functional alterations caused by the FAAH SNP remain to be fully characterized, limiting further mechanistic interpretation of these data; however, this novel observation opens the door for more detailed studies in the future.

Though these findings support the general hypothesis that the endocannabinoid system may be relevant in the pathophysiology of IBS, some caution is warranted. Given the small number of individuals homozygous for this SNP, the small numbers of patients included in this genetic association study, and the fact that significance testing is performed against the mixed heterozygous/homozygous group and not against homozygotes only, these observations have to be regarded as preliminary. It is worth mentioning that these genetic findings are unique to IBS; in patients with IBD no such genetic associations were identified.[94] Whether reported SNPs in the CB_1 or CB_2 receptor genes are also associated with changes in gastrointestinal function is presently unknown.

OUTLOOK

It is too early to speculate whether or not the endocannabinoid system is involved in the pathophysiology of IBS. However, there are many potential components in this system and whether through endocannabinoid deficiency,[112] specific CB receptor defects, enzyme defects affecting endocannabinoid synthesis or breakdown, the endocannabinoid system could contribute to the symptoms of IBS. For certain factors implicated in the pathophysiology of IBS, such as altered motility, for example, involvement of the endocannabinoid system appears plausible and pharmacological targeting of the endocannabinoid system may be beneficial. On the other hand, the role of the endocannabinoid system in other circuits potentially involved in the pathophysiology of IBS is not well understood. For example, it is unknown whether the endocannabinoid system plays a role in the psychosocial dimensions of IBS. Furthermore, although the endocannabinoid system is involved in stress responses in laboratory animals, it is not known whether it is involved in emotional stress, a well-known exacerbating factor in the symptom severity of many IBS patients. Recent evidence supporting an important role for the endocannabinoid system in the pathophysiology of at least one form of IBS warrants further investigation.[107] A summary of the potential role of the endocannabinoid system in IBS is shown in Fig. 2.

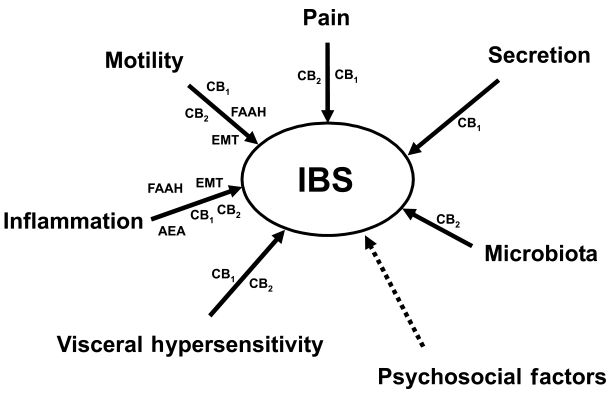

Figure 2 Possible roles of the endocannabinoid system in irritable bowel syndrome (IBS). The endocannabinoid system is involved in the regulation of many of the factors that have been implicated in the pathophysiology of IBS. The arrows indicate each of these factors and the components of the endocannabinoid system supported by current evidence that influence the respective function, and thus might be targeted to treat IBS. Anandamide (AEA), endocannabinoid membrane transporter (EMT), fatty acid amide hydrolase (FAAH). The dashed arrow indicates no current information.

Besides exploring the role of the endocannabinoid system in the pathophysiology IBS, cannabinoid agents might be treatment options for IBS patients by targeting the underlying alterations in motility, inflammation, pain and sensation. Clinical trials would be helpful in elucidating the potential benefit of cannabinoid drugs in IBS.

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