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REVIEW

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The endocannabinoid system in the physiology and pathophysiology of the gastrointestinal tract

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Abstract Numerous investigations have recently demonstrated the important roles of the endocannabinoid system in the gastrointestinal (GI) tract under physiological and pathophysiological conditions. In the GI tract, cannabinoid type 1 (CB1) receptors are present in neurons of the enteric nervous system and in sensory terminals of vagal and spinal neurons, while cannabinoid type 2 receptors are located in immune cells. Activation of CB1 receptors was shown to modulate several functions in the GI tract, including gastric secretion, gastric emptying and intestinal motility. Under pathophysiological conditions induced experimentally in rodents, the endocannabinoid system conveys protection to the GI tract (e.g. from inflammation and abnormally high gastric and enteric secretions). Such protective activities are largely in agreement with anecdotal reports from folk medicine on the use of *Cannabis sativa* extracts by subjects suffering from various GI disorders. Thus, the endocannabinoid system may serve as a potentially promising therapeutic target against different GI disorders, including frankly inflammatory bowel diseases (e.g. Crohn's disease), functional bowel diseases (e.g. irritable bowel syndrome) and secretion- and motility-related disorders. As stimulation of this modulatory system by CB1 receptor agonists can lead to unwanted psychotropic side effects, an alternative and promising avenue for therapeutic applications resides in the treatment with CB1 receptor agonists that are unable to cross the blood–brain barrier, or with compounds that inhibit the degradation of endogenous ligands (endocannabinoids) of CB1 receptors, hence prolonging the activity of the endocannabinoid system.

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Abbreviations Anandamide: arachidonoyl ethanolamide · 2-AG: 2-arachidonoyl glycerol · AT: anandamide transporter · CB1: cannabinoid type 1 · CB2: cannabinoid type 2 · FAAH: fatty acid amide hydrolase · GI: gastrointestinal · Δ^9-THC: delta-9-tetrahydrocannabinol · TRPV1: vanilloid type 1 · CCK: cholecystokinin

Introduction

For centuries, different preparations of *Cannabis sativa* plants have been used for the treatment of gastrointestinal (GI) disorders such as GI pain, gastroenteritis and diarrhoea [1]. *C. sativa* extracts contain more than 60 different cannabinoid-like compounds. Since the isolation of delta-9-tetrahydrocannabinol (Δ^9-THC), the major psychoactive component of cannabis, a broad range of synthetic and endogenous cannabinoids have been characterized and used to assign the various roles of the endocannabinoid system to physiological processes in the GI tract, including the modulation of GI motility, gastric secretion and gastric emptying [2, 3].

Endocannabinoids are lipids that are able to act on two different seven-transmembrane G-protein-coupled receptors, called cannabinoid type 1 (CB1) and cannabinoid type 2 (CB2) receptors [4, 5]. CB1 receptors are highly expressed in the central and peripheral nervous systems, but non-neuronal expression sites such as adipocytes and endothelial cells have also been described [6, 7]. In neurons, endocannabinoids act mainly presynaptically, modulating the transmission of other neurotransmitters including γ-aminobutyric acid, glutamate and acetylcholine. In contrast to "classic" neurotransmitters, they are not stored in vesicles, but they are synthesized on-demand from membrane precursors. CB2 receptors are predominantly but not exlusively present in immune cells, suggesting that endocannabinoids have roles as immunomodulators [8]. In non-neuronal tissues, endocannabinoids may act as hormone-like messengers in an autocrine or paracrine mode of action, which is thought to be, however, spatially and temporally restricted. Thus, they strongly differ in this feature from "classic" hormones.

This review will focus on the roles of the endocannabinoid system in the GI tract—a subject also covered in other recent publications [2, 3, 9–11]. In addition, the authors would like to refer to other reviews on the biochemistry of receptors and ligands and the physiological/pathophysiological roles outside of the GI tract [12–14].

Regarding GI functions, CB1 receptors appear to play the dominant role and will be the focus of this review. In contrast, there is only scarce information on the function of CB2 in the GI tract. It is noteworthy that CB2 receptors in the rat intestine are involved in reducing the increase of intestinal motility enhanced by an endotoxic inflammation [9, 15].

Constituents of the endocannabinoid system and its pharmacological modulation

The CB1 receptors are coupled to $G_{i/o}$ heterotrimeric G proteins [14]. After the binding of ligands, CB1 receptors mediate effects, including the inhibition of adenylyl cyclase [16] and the stimulation of extracellular-regulated kinases [17], protein kinase B (also called Akt) [18], p38 kinase [19] and Jun N-terminal kinase [20]. Cannabinoids acting at CB1 receptors can furthermore inhibit inwardly rectifying potassium channels and voltage-dependent A-type potassium channels, eventually leading to an increased efflux of K^+ ions. Moreover, $G_{i/o}$ activated by CB1 receptors can directly inhibit N- and P/Q-type calcium channels, thus decreasing Ca^{2+} ion influx into the cell [14, 21, 22]. Both these features will lead to a reduced excitability of the neurons after CB1 receptor activation (Fig. 1).

Several endogenous agonists for cannabinoid receptors have been characterized to date, but the best characterized endocannabinoids so far are arachidonoyl ethanolamide (anandamide) and 2-arachidonoyl glycerol (2-AG). Both are produced on-demand from membrane-associated precursors involving phospholipases D and C. The structurally related compounds palmitoylethanolamide and oleoylethanolamide have distinct functions in the GI tract, although they do not bind to CB1 receptors [23–25]. Apart from

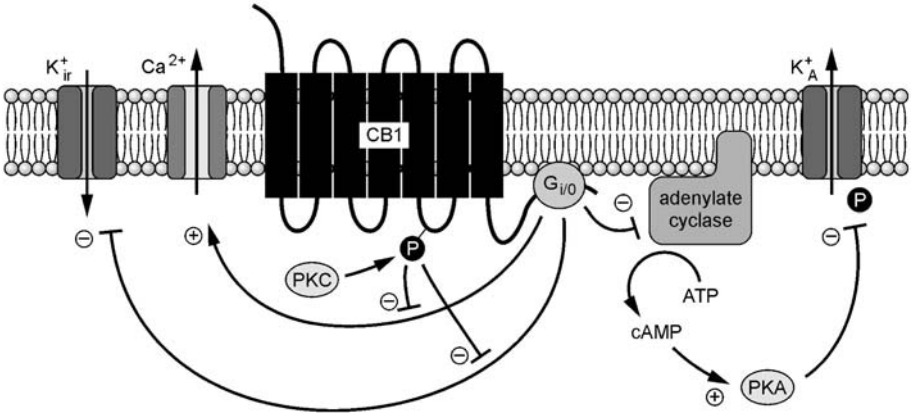

Fig. 1 Schematic representation of the main effects of CB1 receptors on ion channels. The activation of CB1 receptors leads to the stimulation of $G_{i/o}$ proteins that inhibit the adenylyl-cyclase-mediated conversion of adenosine triphosphate into cyclic adenosine monophosphate, which binds to the regulatory subunits of protein kinase A and causes the liberation of catalytic subunits, which then phosphorylate A-type potassium channels (K_A^+), causing a decrease in K^+ efflux. Given the negative effect of CB1 on adenylyl cyclase, the final result is an activation of A-type potassium channels. $G_{i/o}$ activated by CB1 can also directly inhibit N- or P/Q-type calcium channels and activate inwardly rectifying potassium channels (K_{ir}). The latter two effects are regulated by protein kinase C, which can phosphorylate CB1 receptors in the third cytoplasmic loop and uncouple the receptor from the ion channels

binding to cannabinoid receptors, anandamide and 2-AG are also able to activate vanilloid type 1 (TRPV1) receptor [7, 25–27]. Recently, anandamide has been proposed to interact directly with other molecular targets including non-CB1 receptors, non-CB2 receptors, G-protein-coupled receptors and ion channels such as TASK1 and receptors of yet unknown identity [28–30].

Exogenous compounds binding to cannabinoid receptors can be divided into several classes (Fig. 2). The so-called "classic" cannabinoid receptor agonists are structurally closely related to Δ^9-THC, with the tricyclic dibenzopyran structure serving as a lead structure. The most widely used compounds of this class are Δ^9-THC and HU210. "Nonclassic" cannabinoids (i.e. THC derivatives lacking the dihydropyran ring) include CP55,940 (developed by Pfizer), a compound that was instrumental in the initial biochemical characterization of CB1 receptors. Lastly, WIN55,212-2 belongs to the aminoalkylindole family, which is structurally unrelated to Δ^9-THC. However, like anandamide, this compound, which is a highly potent cannabinoid receptor agonist, is also able to inhibit TASK1 [29] and to activate yet unidentified non-CB1/non-CB2 G-protein-coupled receptors [31]. Δ^9-THC, HU210, CP55,940 and WIN55,212-2 have a high efficacy on both CB1 and CB2 receptors [32]. To study the roles of the endocannabinoid system, specific agonists and antagonists of CB1 and CB2 receptors, respectively, have been developed. CB1-receptor-specific agonists are ACEA and ACPA [33], while CB2-specific agonists include AM1241 [34], L-759633 [35], L-759656 [35], JWH-133 [25] and HU-308 [36]. Potent CB1-receptor-selective antagonists are SR141716 (recently called rimonabant) [37], SR14778 [38], AM251 [39], AM281 [40], SLV319 [41] and LY320135 [42]. CB2-receptor-selective antagonists are SR144528 [43] and AM630 [44]. Due to the increased interest in the pharmacological targeting of the endocannabinoid system in the context of various human pathologies, the list of synthetic agonists/antagonists will certainly grow in the very near future [13, 45].

Physiological endocannabinoid signalling is terminated by specific degradation systems involving the uptake of endocannabinoids into the cell by a facilitated endocannabinoid transport mechanism and the hydrolysis by fatty acid amide hydrolase (FAAH) for anandamide and by monoacylglycerol lipase for 2-AG, respectively [46, 47] (Fig. 3). To date, several synthetic compounds have been shown in in vivo studies to efficiently block endocannabinoid uptake (AM404, VDM11, UCM707 and OMDM-2) [48] or anandamide degradation (URB597 and AA-5-HT) [49, 50], thus providing a pharmacological tool to enhance the activity of the endocannabinoid system and avoiding the "direct" stimulation of cannabinoid receptors with agonists, which would lead to undesirable psychotropic effects.

The endocannabinoid system in the GI tract

For the first time in 1995, the endocannabinoid 2-AG was isolated from canine intestine [51]. Much later, anandamide was isolated in the small intestine of mice [52]. The anandamide-degrading enzyme FAAH was characterized in mouse [53] and rat [54] intestines. Different functional studies provided evidence for an anandamide transporter (AT) in the GI tract [53, 55]. CB1 receptors were found in the GI tract of different species, including mice, rats, guinea pigs, pigs and humans [56–59]. Immunohistochemical studies demonstrated the presence of CB1 protein in the enteric nervous system, specifically in neurons and fibres in the myenteric and submucosal plexuses [56], while electrophysiological studies provided functional evidence of the existence of prejunctional CB1 receptors in the human ileum longitudinal smooth muscle [58] (Fig. 4).

On the other hand, CB2 receptor messenger ribonucleic acid (mRNA) was found primarily in immune cells, including rat peritoneal mast cells [60]. This expression is possibly important during inflammatory processes in the GI tract [9].

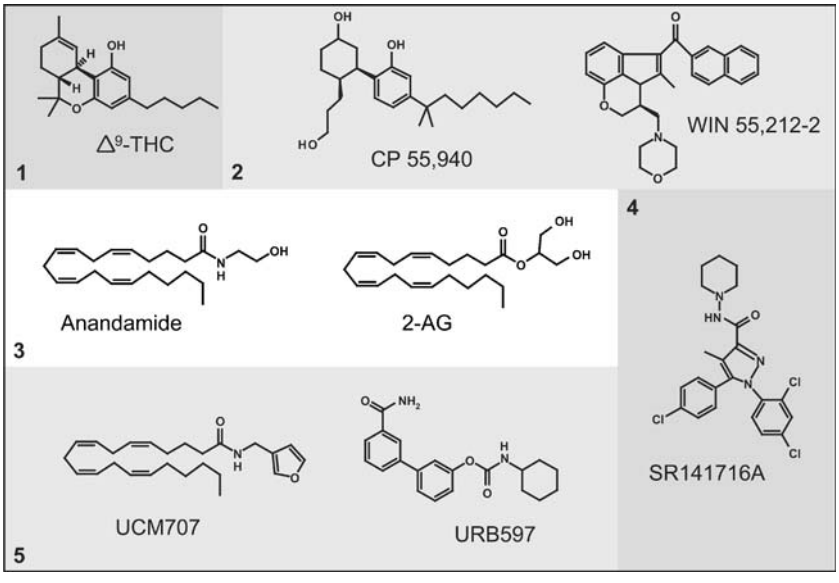

Fig. 2 Chemical structures of different CB1 agonists/antagonists and inhibitors of endocannabinoid inactivation. *1* The "classic" cannabinoid Δ^9-THC; *2* the "nonclassic" cannabinoid CP55,940 and the aminoalkylindole WIN55,212-2; *3* the endocannabinoids anandamide and 2-arachidonoylglycerol; *4* the selective CB1 antagonist SR141716; and *5* the anandamide transporter inhibitor UCM707 and the FAAH inhibitor URB597

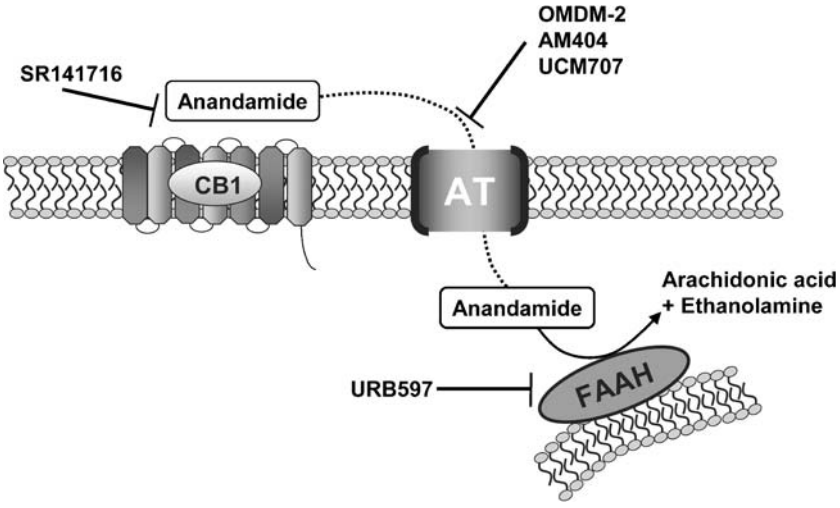

Fig. 3 Scheme of anandamide inactivation. The on-demand release of anandamide leads to the activation of CB1 receptors. Anandamide is degraded intracellularly by the membrane-bound enzyme FAAH. An anandamide receptor (AT) facilitates the uptake of anandamide into the cell. OMDM-2, AM404 and UCM707 are inhibitors of AT, while URB597 inhibits FAAH

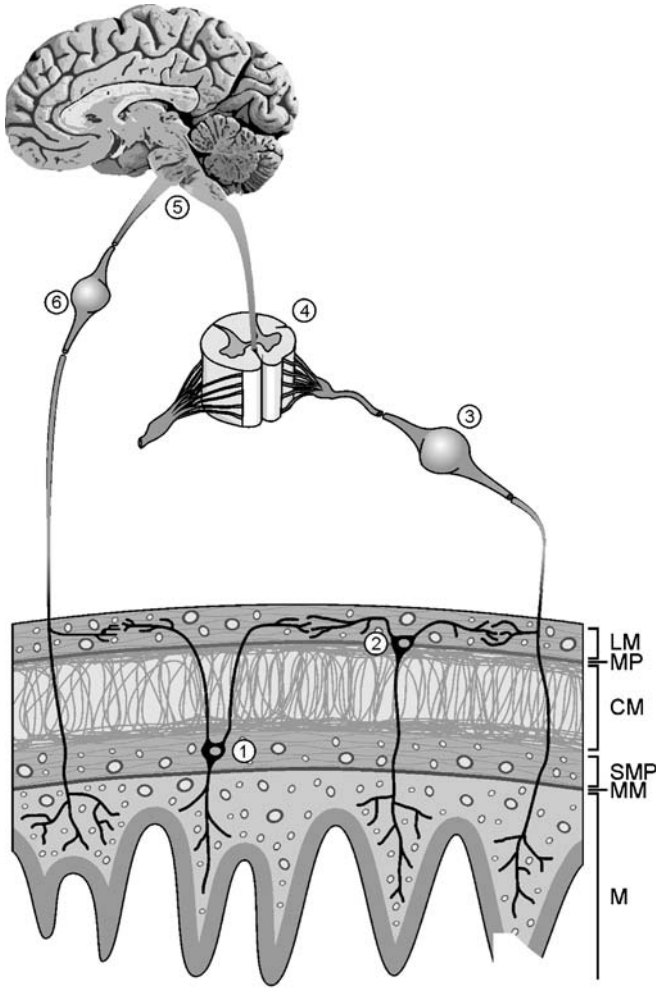

Fig. 4 Localization of CB1 receptors in the GI tract and sensory efferent neurons. CB1 receptors are localized in sensory neurons, *1* in the submucosal plexus (SMP) and *2* in the myenteric plexus (MP) of the enteric nervous system. CB1 receptors are also present in *3* sensory neurons of the dorsal root ganglia, *4* in the dorsal horn of the spinal cord, *5* in the brainstem and *6* in efferents from the vagal ganglia. These sites of expression modulate the sensory input received from the GI tract. *M* Mucosa, *MM* muscolaris mucosae, *CM* circular muscle, *LM* longitudinal muscle

Moreover, experiments performed on the guinea pig small intestine [61] demonstrated the presence of CB1 and CB2 receptor mRNA in this tissue. While the CB1 receptor was also detected in myenteric plexus preparation, Griffin et al. noted the presence of the CB2 receptor only in the whole segment of the intestine, suggesting that blood cells account for the presence of the CB2 receptor. In the mouse gut, the CB1 receptor protein was detected by immunoblotting with a differential expression along the various segments of the gut [59].

In the gut, CB1 receptors are widely colocalized with acetylcholine transferase, which is a marker for cholinergic neurons. This observation supports the role of endocannabinoids as inhibitors of intestinal motility and secretion [10] by presumably inhibiting cholinergic neurotransmission in the GI tract. CB1 receptors are partly colocalized with substance P immunoreactive intestinal neurons but not with nitric oxide synthase immunoreactive neurons or fibres [57, 62, 63].

Finally, immunohistochemical studies revealed that some neurons containing δ-opioid-receptor-like immunoreactivity are also immunoreactive for κ-opioid, CB1 and TRPV1 receptors. These observations indicate that these receptor systems may interact with one another to modulate intestinal sensorimotor function in the myenteric plexus [62].

Pharmacological effects of cannabinoids and the roles of the endocannabinoid system during physiological and pathophysiological processes in the GI tract

One of the most peculiar characteristics of the endocannabinoid system is its highly selective spatial and temporal specificity of activation. Synthesis, release, activation of receptors and eventual degradation of endocannabinoids are thought to occur on-demand, where and when appropriate conditions are reached during physiological and pathophysiological processes [12, 13]. Therefore, generalized treatments with cannabinoid agonists (natural, synthetic or endogenous) do not always mimic the physiological and

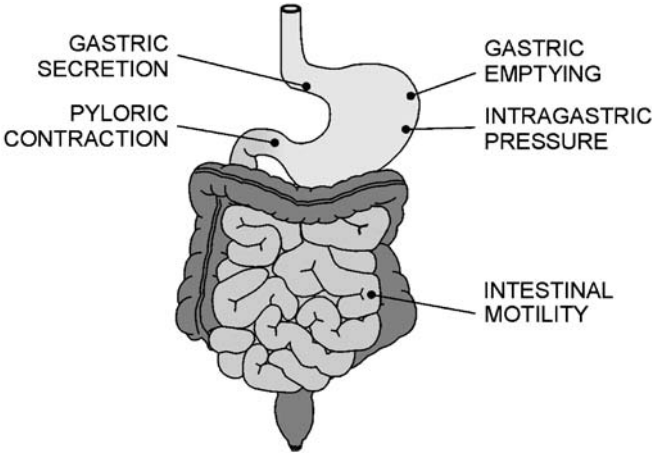

Fig. 5 Sites of action where the pharmacological modulation of the endocannabinoid system represents a promising therapeutic target

pathophysiological functions of the system. However, a large body of data has recently demonstrated that endocannabinoids play different important roles in GI physiology (Fig. 5) [3, 11].

Most of the experiments were designed to investigate the pharmacological effects of cannabinoid agonists on GI functions. Only a few studies aimed at understanding the physiological or pathophysiological activation of the endocannabinoid system. However, such endogenous activation of the system can be outlined by treatments interfering with the endocannabinoid system (i.e. use of mutant mice lacking elements of the endocannabinoid system [CB1 or FAAH], treatment with specific antagonists in the absence of agonist or treatment with inhibitors of endocannabinoid degradation and/or uptake).

Roles in the physiology of the GI tract

Motility

Endogenous and synthetic cannabinoids are able to inhibit, in a CB1-receptor-dependent manner, electrically evoked contractions in the isolated guinea pig small intestine [55, 64], although cannabinoids appear not to be able to modify the contractions induced by a direct application of exogenous acetylcholine, which is responsible for promoting the contraction of intestinal smooth muscles via postjunctional muscarinic receptors [55]. Interestingly, Mang et al. [65] demonstrated that anandamide inhibits the electrically evoked release of acetylcholine acting on CB1 receptors and, at the same time, acts on TRPV1 receptors, leading to an increase of basal levels of acetylcholine. Recently, the role of anandamide in the control of intestinal motility during physiological and pathophysiological states has been investigated. Capasso et al. [66] demonstrated that intestinal motility is inhibited by selective FAAH inhibitors and that this effect is reduced by CB1 receptor antagonists, but not by TRPV1 receptor antagonists. Mascolo et al. showed that the intestinal hypomotility typical of paralytic ileus is due, at least in part, to the enhancement of anandamide levels and CB1 expression during this condition, demonstrating that acetic-acid-induced ileus was alleviated by the CB1 receptor antagonist SR141716A and worsened by VDM11, a selective inhibitor of anandamide cellular uptake [67].

Gastric emptying and intestinal motility

Intravenous Δ^9-THC administration was demonstrated to slow down the rate of gastric emptying and small intestine motility in rodents [68] and humans [69]. Δ^9-THC and cannabinol also inhibited intestinal motility in mice, but were less effective in reducing gastric emptying [70]. These results were also confirmed by the use of the CB1 agonists WIN55,212-2 and CP55,940 and blocked by the selective CB1 antagonist SR141716 [71, 72], proving that these effects are mediated by the CB1 receptor, although, until today, no evidence has suggested a direct role of the CB1 receptor on parietal cells. Moreover, Krowicki et al. [73] demonstrated that intravenous administration of Δ^9-THC evokes long-lasting decreases in intragastric pressure and pyloric contractility. These changes in gastric motor function were abolished by vagotomy, ganglionic blockade and CB1 antagonism with SR141716.

Recently, the role of CB2 receptors in the control of GI motility was investigated [15]. Lipopolysaccharide treatment increased GI motility. This increased motility was reduced to control values by a CB2 agonist, but not by a CB1 agonist. This inhibition by the CB2 agonist was dose-dependent and was prevented by a selective CB2 antagonist. The authors suggested that the stimulation of CB2 receptors in response to lipopolysaccharide might be a mechanism for the reestablishment of normal GI motility after an inflammatory stimulus.

Gastric acid secretion

Several studies demonstrated the role of the endocannabinoid system in the regulation of gastric acid secretion. In isolated stomach preparations from rats, Δ^9-THC was able to counteract histamine-induced secretion, but only at high doses [74]. WIN55,212-2 and HU210 were able to inhibit, via a peripheral mechanism, gastric secretion induced by pentagastrin in rats. These effects were blocked by CB1 receptor antagonists [3, 75, 76] and indicated that the gastric antisecretory effects of cannabinoids might be mediated by the activation of CB1 receptors, located on preganglionic and postganglionic cholinergic pathways [76].

Feeding behaviour

Several studies suggested that the endocannabinoid system can modulate food intake via cannabinoid receptors in the brain and in the periphery [77]. Gomez et al. [78] demonstrated that CB1 receptors can modulate food intake by acting selectively on capsaicin-sensitive sensory terminals,

revealing an unexpected role for peripheral CB1 receptors in the regulation of feeding.

Roles in the pathophysiology of the GI tract

Presently, there is great effort to characterize the role of the endocannabinoid system in GI physiology. Whereas major progress is apparent, there is still a lack of knowledge on the involvement of the endocannabinoid system in pathophysiological states.

There is a growing body of evidence suggesting that cannabinoids are helpful in a variety of GI dysfunctions in humans. Anecdotal and patient reports suggest that states of diarrhoea and abdominal cramping might be treated with cannabinoid extracts [1]. Presently available knowledge on the possible or likely involvement of cannabinoids in diseases of the GI tract is summarized below.

Emesis

In humans, the antiemetic and antinauseous effects of cannabinoids are well established by clinical investigations in cancer patients receiving chemotherapy or radiation therapy, or in patients receiving human immunodeficiency virus therapy [79, 80]. Animal studies suggest the involvement of central as well as peripheral sites. Central sites involve the area postrema and the dorsal vagal complex, whereas for the peripheral effects, vagal efferents are involved [81–83]. Interestingly, cannabinoids cause a delay of gastric emptying [69], which per se would cause nausea, suggesting that the central effects might be more important than peripheral effects in reducing nausea and emesis.

To date, nausea and emesis due to malignancies are the only proven indications for cannabinoids within GI pathologies. More than 40 clinical studies verified the beneficial effects and, only for the treatment of acute chemotherapy-induced emesis, serotonin receptor antagonists are superior compared to CB1 receptor agonists [2, 79].

Acid-related disorders

An excess of gastric acid production can lead to gastritis and ulceration of the stomach or duodenum. CB1 receptors located on vagal efferent pathways seem to be involved in mediating the reduction of stimulated gastric acid production [76]. Although CB1 receptor agonists do not directly reduce the histamine-stimulated acid production of parietal cells, CB1 receptor activation reduces local histamine release from enterochromaffin cells [74]. This would cause a reduction of acid production, although this final step has not been reported for CB1 receptor agonists. This possible dual mode of gastric acid reduction may be the underlying mechanism for the CB1-receptor-mediated antiulcer activity reported in a rat ulcer model [84]. Whether these effects may be used clinically remains speculative; observations in humans suggest that cannabis consumption reduces gastric acid production, although an exact evaluation in humans is still missing.

Besides ulcerative disease, gastric acid is also involved in gastro-oesophageal reflux disease (GERD). Up to the present, transient lower oesophageal sphincter relaxations (TLESRs) are believed to be a major cause underlying GERD [85]. TLESRs are characterized by a swallow-independent and continuous relaxation of the lower oesophageal sphincter, with a rapid onset. Cannabinoid agonists (Δ^9-THC and WIN55,212-2) reduced TLESR in ferrets and dogs, both in total occurrence and in amplitude, by CB1-receptor-dependent mechanisms. Central and peripheral vagal mechanisms are involved in these functional changes [86, 87]. Whether this finding may be used for the treatment of GERD as a single or combination treatment has to be further characterized, but the dual mode (TLESR reduction and acid suppression) by which CB1 agonists may have beneficial effects on GERD treatment merits further investigations.

Motility-related disorders

Properties of the endocannabinoid system relevant to the reduction of intestinal motility were discussed earlier. Although, at the moment, no clinical studies are available, CB1 agonists or a stimulation of the endocannabinoid system, by using degradation inhibitors, might represent a possible target in motility disorders characterized by hypercontractile states.

On the other hand, there is strong evidence that CB1 receptor antagonists cause increased GI motility, most likely by inhibiting the stimulation of CB1 receptors, although an auxiliary, inverse agonist activity of the CB1 antagonists is also discussed [3]. This means that antagonists at CB1 receptors might be helpful pharmacological tools in the treatment of motility disorders where hypomotility is the symptom (e.g. obstipation).

In vivo studies strengthen further the notion that not only peripheral but also central sites of action are involved [2]. Whether or not these central sites of action are really useful in this context has to be evaluated as central CB1 receptors mediate unwanted psychotropic side effects. The involvement of additional receptors mediating cannabinoid effects on motility is uncertain, but the finding that palmitoylethanolamide (an endocannabinoid-like compound binding neither to CB1 nor CB2 receptors) exerts similar effects on motility as a CB1 receptor agonist makes this option likely [23]. Although TRPV1 receptors emerge as hot candidates [53], the effect of anandamide on intestinal motility in physiological conditions seems not to be mediated by TRPV1 receptors [88], while the nature of the additional receptor(s) remains speculative. Nevertheless, it is worthwhile trying to unmask such a putative receptor since it might be free of unwanted CB1-receptor-associated side effects.

Diarrhoea and irritable bowel syndrome

Historical documents describe that cannabinoids were used for the treatment of diarrhoea and abdominal cramping in ancient cultures but also in the developed countries until approximately 1920.

Motility-modifying effects support these indications, but evidence based on clinical studies is missing. Apart from motility effects, cannabinoids reduce intestinal secretion and increase the resorption of electrolytes and water, which might be beneficial in secretory diarrhoea. These effects on secretion are mediated via CB1 receptors on a peripheral neuronal site. Cholinergic as well as noncholinergic mechanisms are modulated by CB1 receptors [89, 90], and an epithelial site of action has not been reported. An unsolicited observation in cannabis consumers who had contact with *Vibrio cholerae* reports an attenuated course of concomitant diarrhoea [91]. Moreover, Izzo et al. [92] demonstrated that cannabinoid receptor agonists were able to inhibit fluid accumulation in a cholera toxin model of secretory diarrhoea in mice, and that this effect was counteracted by the CB1 receptor antagonist SR141716.

Irritable bowel syndrome (IBS) might be counteracted by cannabinoids, at least the motility-related symptoms, where cannabinoids could reduce muscle spasms underlying the symptom of abdominal pain [93]. Whether this holds true in clinical trials and whether possible antinociceptive and antihyperalgesic effects of cannabinoids are involved remain highly speculative as, presently, no evidence for such effects within the GI tract is available.

Inflammatory bowel diseases

During the last decade, several experimental animal models of inflammatory bowel diseases have been developed to define the different components of the pathophysiological processes characterizing these disorders. Evidence for cannabinoid involvement in the control of intestinal function exists for the small and large intestines. In croton-oil-induced inflammation of the mouse small intestine, an increase of CB1 receptor activity was observed [52]. In the inflamed state, the delay of motility following exogenous cannabinoid receptor agonists was more pronounced, consistent with the increased CB1 receptor expression observed. However, the levels of anandamide and 2-AG in the inflamed tissue were not increased, suggesting a more rapid turnover of endocannabinoids—a notion that is stressed by the finding that the expression of the anandamide-degrading enzyme FAAH is increased in the inflamed tissue [52]. Presently, the finding that levels of palmitoylethanolamide are decreased is unclear, and it remains speculative whether or not this reduction underlies the increased intestinal motility during inflammation [23]. The report that indomethacin-induced inflammation of the small intestine is prevented by SR141716, probably in a CB1-independent manner, indicates that the role of the endocannabinoid system in inflammatory states is not yet fully understood [94].

Experiments in CB1-deficient mice showed the importance of this receptor in colitis induced by dextrane sodium sulphate and dinitrobenzenesulphonic acid, as the inflammation was more fulminant in the CB1-deficient animals and the expression of CB1 receptors was increased in colitis compared to wild-type littermates [95]. This report stresses the potentially pathophysiological involvement of the endocannabinoid system in inflammatory states of the gut. Importantly, the phenotype of CB1-deficient mice was reproduced by the treatment of wild-type mice with the CB1 antagonist SR141716, indicating an acute activation of the endocannabinoid system during the inflammatory process. Moreover, in wild-type mice, colitis is reduced by the application of the cannabinoid receptor agonist HU210. For future therapeutic options, it is interesting to observe that, in FAAH-deficient mice, where increased levels of endocannabinoid are present, colitis takes a milder course, further supporting the protective activation of the endocannabinoid system during colitis. This strongly suggests FAAH inhibitors as possible pharmacological tools for the treatment of inflammatory states.

Cancer

To date, cannabinoids are well-established drugs for supportive treatment in cancer therapy. Specific preparations, normalized for Δ^9-THC contents, are prescribed to alleviate cancer- or cancer-treatment-related symptoms such as nausea, vomiting, cachexia or loss of appetite [96]. Apart from this symptomatic benefit, there is evidence from regions other than the GI tract that the endocannabinoid system might be involved in cancer differentiation, growth and cell migration, which are important processes in the development of metastasis [97]. For the GI tract, CB1 and CB2 receptor mRNA are expressed in the human normal colonic mucosa, adenomatous polyps and carcinomas. Cannabinoid receptor agonists potently inhibit the cell proliferation of colorectal carcinoma cell lines that express CB1 receptors (e.g. CaCo2 cells). This effect is blocked by the CB1 receptor antagonist SR141716 but not by the CB2 receptor antagonist SR144528, suggesting a specific involvement of CB1 receptors [97]. Additionally, endocannabinoid levels are enhanced in transformed colonic mucosa cells, which might mean that these compounds are elevated to possibly counteract proliferation via the activation of cannabinoid receptors. These findings are promising and consistent with other models of neoplasia research, but it is premature to suggest a role of the endocannabinoid system in GI malignant diseases.

Interaction with other systems

Opioids

Gastrointestinal sensory nerve fibres are considered to be important targets of novel drugs for the treatment of functional bowel disorders and visceral pain [98]. CB1 and

opioid receptors are colocalized in neurons located in the myenteric and submucosal plexuses [62], and both receptors are involved in the inhibition of visceral perception and are overexpressed in models of intestinal inflammation [52, 95, 98]. During the last decade, a large number of publications have shown a crosstalk between these neuromodulatory systems in the central nervous system [99], but it awaits to be explored whether these two endogenous system have a functional interaction in the gut. However, the effects of CB1 receptor agonists on motility are not counteracted by the opioid antagonist naloxone [88, 100]. Moreover, inflammation-induced enkephalin expression does not appear to be modulated by CB1 receptors during experimentally induced colitis in mice [95].

Cholecystokinin

In the GI tract, both inhibitory and stimulatory factors appear to regulate food intake. The satiety hormone cholecystokinin (CCK) regulates these effects via vagal afferent neurons [101]. As CCK is a satiety factor that acts via the vagus nerve and as CB1 agonists stimulate food intake, Burdyga et al. [102] suggested a mechanism modulating the effect of food intake on satiety signals from the GI tract. Vagal afferent neurons expressing the CCK-1 receptor also express CB1 receptors. Retrograde tracing demonstrates that these neurons project to the stomach and duodenum. The expression of CB1 receptors is increased by withdrawal of food. After the refeeding of fasted rats, there is a rapid loss of CB1 receptor expression identified by immunohistochemistry and in situ hybridization. These effects are blocked by the administration of the CCK-1 receptor antagonist lorglumide and mimicked by the administration of CCK to fasted rats.

Endovanilloids

Several studies demonstrated an interaction between these two endogenous systems [28, 103]. Anandamide is able to bind endogenous TRPV1 receptors in different tissues such as sensory neurons in the GI tract [103].

It is noteworthy that TRPV1-receptor-expressing sensory neurons tested in vitro contain CB1 receptors as well [104], which might suggest that anandamide controls excitability and neurotransmission in primary sensory neurons. Recently, Ahluwalia et al. [105] demonstrated that anandamide controls the release of calcitonin gene-related peptide, a neurogenic mediator during inflammation, in capsaicin-expressing sensory neurons in vivo, and this release depends on the concentration of anandamide and CB1 and TRPV1 receptor functions.

Conclusions

The role of the endocannabinoid system in the control of GI functions under physiological and pathological conditions has recently received increased interest. Within the last 5 years, more than half of all studies on the roles of the endocannabinoid system in the GI tract have been published. The current state of knowledge of the physiology and pharmacology of cannabinoids has largely increased, providing new potential tools for the treatment of several GI diseases. The symptoms of the most common GI disorders, IBS and inflammatory bowel disease, affect more than 20% of the population in Western countries and cause great discomforts [106]. Intestinal cramping, nausea, chronic diarrhoea and inflammation are all symptoms onto which the cannabinoids may be effective. Cannabis derivatives and other newly developed cannabinoids may represent promising tools for the treatment of different GI disorders because they can act at multiple sites, covering a wide spectrum of symptoms. In fact, the endocannabinoid system is able to modulate not only gut physiology but also the crosstalk between the gut and the brain. In this context, it is important to note that, in several GI diseases, the endocannabinoid system appears to be activated with the aim of counteracting pathological outcomes. Therefore, the use of drugs able to "help" the physiological activation of the endocannabinoid system (i.e. inhibitors of endocannabinoids degradation) could provide very specific tools to treat GI disorders, avoiding most of the unwanted central side effects of CB1 agonists. Moreover, such side effects may be avoided by the development of new cannabinoids unable to cross the blood–brain barrier.

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