Endocannabinoids and the Digestive Tract and Bladder in Health and Disease

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R.G. Pertwee (ed.), *Endocannabinoids*, Handbook of Experimental Pharmacology 231, DOI 10.1007/978-3-319-20825-1_15

Abstract

Components of the so-called endocannabinoid system, i.e., cannabinoid receptors, endocannabinoids, as well as enzymes involved in endocannabinoid synthesis and degradation, have been identified both in the gastrointestinal and in the urinary tract. Evidence suggests that the endocannabinoid system is implicated in many gastrointestinal and urinary physiological and pathophysiological processes, including epithelial cell growth, inflammation, analgesia, and motor function. A pharmacological modulation of the endocannabinoid system might be beneficial for widespread diseases such as gastrointestinal reflux disease, irritable bowel syndrome, inflammatory bowel disease, colon cancer, cystitis, and hyperactive bladder. Drugs that inhibit endocannabinoid degradation and raise the level of endocannabinoids, non-psychotropic cannabinoids (notably cannabidiol), and palmitoylethanolamide, an acylethanolamide co-released with the endocannabinoid anandamide, are promising candidates for gastrointestinal and urinary diseases.

Keywords

2-Arachydonoylglycerol • Anandamide • Bladder • Cancer • Cannabidiol • Cannabinoid receptors • Cystitis • Fatty acid amide hydrolase • Inflammation • Monoacylglycerol lipase • Palmitoylethanolamide • Transient receptor potential channels

Abbreviations

2-AG	2-Arachidonoylglycerol
ABHD6	α/β-Hydrolase domain-containing protein 6
ACEA	Arachidonyl-2-chloroethylamide
AEA	Arachidonoyl ethanolamide
ATP	Adenosine triphosphate
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBC	Cannabichromene
CBD	Cannabidiol
CBDV	Cannabidivarin
CBG	Cannabigerol
CD	Crohn's disease

CGRP	Calcitonin gene-related polypeptide
CNS	Central nervous system
COX	Cyclooxygenase
DRG	Rat dorsal root ganglia
DVC	Dorsal vagal complex
EDTA	Ethylenediaminetetraacetic acid
EFS	Electric field stimulation
ENS	Enteric nervous system
EP1	Prostaglandin E receptor 1 (subtype EP1)
FAAH	Fatty acid amide hydrolase
GI	Gastrointestinal
GPR119	G protein-coupled receptor 119
GPR55	G protein-coupled receptor 55
IBD	Inflammatory bowel diseases
IBS	Irritable bowel syndrome
IHC	Immunohistochemistry
LES	Lower esophageal sphincter
LPS	Lipopolysaccharide
MAGL	Monoacylglycerol lipase
NAAA	N-acylethanolamine-hydrolyzing acid amidase
NAE	N-acylethanolamine
NAPE-PLD	N-acyl phosphatidylethanolamine phospholipase D
OEA	Oleoylethanolamide
PEA	Palmitoylethanolamide
PPARs	Peroxisome proliferator-activated receptors
PPARα	Peroxisome proliferator-activated receptor α
PPARγ	Peroxisome proliferator-activated receptor γ
THC	Δ^9-Tetrahydrocannabinol
THCV	Δ^9-Tetrahydrocannabivarin
TNF-α	Tumor necrosis factor alpha
TRP	Transient receptor potential channels
TRPM8	Transient receptor potential cation channel subfamily M member 8
TRPV1	Transient receptor potential vanilloid 1
TRPV4	Transient receptor potential vanilloid 4
UC	Ulcerative colitis
WB	Western blot

1 Introduction

Cannabis preparations have been used to treat a variety of gastrointestinal conditions that range from inflammatory and infective conditions to disorders of motility, secretion, abdominal pain, and emesis (Nocerino et al. 2000; Grinspoon and Bakalar 1995). Furthermore, anecdotal reports from patients with multiple

sclerosis have suggested that preparations from the plant *Cannabis sativa* might have a beneficial effect on lower urinary tract symptoms. The pharmacological basis of these empirical/traditional uses emerged after the discovery, in the early 1960s, of Δ^9-tetrahydrocannabinol (THC) as the major bioactive constituent of *Cannabis* and in the 1990s, with the identification of cannabinoid (CB_1 and CB_2) receptors, of the endogenous ligands that activate them, initially the endocannabinoids anandamide and 2-arachidonoylglycerol (2-AG), and of the enzymes involved in the biosynthesis and degradation of endocannabinoids.

This article presents an overview on the pharmacology and potential therapeutic applications of cannabinoids in the gut and in the lower urinary tract

2 The Endogenous Cannabinoid System in the GI Tract

The gastrointestinal (GI) tract is a complex system which requires the interaction of numerous different cell types including epithelial cells, glandular cells, muscle cells, neurons, and of course gut microbiota. Studies over the years have demonstrated that endocannabinoids play a pivotal role in maintaining the homeostasis of the GI tract (Izzo and Sharkey 2010; Alhouayek and Muccioli 2012).

Two lipid mediators, the *N*-acylethanolamine (NAE) anandamide and the acylglycerol 2-arachidonoylglycerol (2-AG), are at the center of the endocannabinoid system. They are both synthesized on demand from membrane lipid precursors. Although multiple pathways have been described, the key enzyme in anandamide production is phospholipase D (NAPE-PLD), whereas the key enzymes in 2-AG production are diacylglycerol lipase α and β (Muccioli 2010). Anandamide and 2-AG are both found throughout the intestinal tract. The cannabinoid (CB) receptors 1 and 2 are the main molecular targets for 2-AG and anandamide, although other receptors, such as transient receptor potential vanilloid 1 (TRPV1) and peroxisome proliferator-activated receptors (PPARs), can play important roles in mediating endocannabinoid effects (Izzo and Sharkey 2010). The CB_1 receptor is expressed in all the GI tract segments, with the highest levels of expression found in the stomach and the colon (Casu et al. 2003). In the colon, it is present in epithelial cells, smooth muscle, and submucosal–myenteric plexus. CB_2 receptor expression is found in immune cells but also in the enteric nervous system (ENS) (Wright et al. 2005; Duncan et al. 2008a).

Fatty acid amide hydrolase (FAAH) is responsible for anandamide catabolism. It is expressed throughout the GI tract, and at similar levels in the different sections of the intestine (Capasso et al. 2005). 2-AG catabolism is mainly mediated by monoacylglycerol lipase (MAGL). This enzyme is expressed from the epithelium to the muscle layers of the gut wall and is also expressed by the enteric neurons. Interestingly its activity decreases from the duodenum to the distal colon (Duncan et al. 2008b).

Although not stricto sensu endocannabinoids, at least two other NAEs—palmitoylethanolamide (PEA) and oleoylethanolamide (OEA)—are important players in the GI tract. Their metabolism is to a certain degree similar to AEA

metabolism. However, PEA and OEA do not bind to the cannabinoid receptors, although they can indirectly activate them via the so-called entourage effect, i.e., the augmentation of the endocannabinoid levels and/or actions at cannabinoid receptors (De Petrocellis et al. 2002). Several PEA and OEA effects are mediated by peroxisome proliferator-activated receptor α (PPARα), including effects on the gut (Fu et al. 2003; Esposito et al. 2014). Nevertheless, PPARα activation is not the only mechanism underlying the effects of OEA and PEA. The G protein-coupled receptor GPR119, activated by OEA (Overton et al. 2006), is one example of the additional molecular targets that are progressively added to the list of players in the endocannabinoid field.

3 The Endogenous Cannabinoid System in the Urinary Tract

There has been great interest in the role of the endocannabinoid system in the regulation of urination since the publication of a beneficial effect of oral administration of *Cannabis* extract on incontinence episodes in patients with multiple sclerosis (Freeman et al. 2006). Because oral administration causes effects on the central nervous system (CNS) as well as on the peripheral structures involved in micturition, it is important to answer the question of whether the beneficial effects are mediated centrally or peripherally. Different in vitro responses to cannabinoid drugs between the rat, mouse, and human bladder suggest that the rat or mouse may not be ideal animal models for the effects of cannabinoid drugs on human bladder function at the end-organ level. It is clear that both CB_1 and CB_2 receptors, as well as FAAH, are expressed in the human bladder, and they may also be involved in sensory pathways governing micturition. The cannabinoid receptors and FAAH are expressed in bladder nerves, dorsal root ganglia, and spinal cord dorsal horn neurons that co-express calcitonin gene-related polypeptide (CGRP), TRPV1, transient receptor potential vanilloid 4 (TRPV4), and purinergic P2X3 receptors. It is not entirely clear whether differences also exist between human and rat or mouse animal models in these sensory mechanisms.

4 Endocannabinoids and the GI Tract: Pharmacology

4.1 Nausea and Emesis

Nausea and vomiting (emesis) are unpleasant conditions of diverse causes, such as infection, chemotherapy, or pregnancy, yet both conditions are highly amenable to cannabinoid treatment (Parker et al. 2011; Sharkey et al. 2014). The regions in the brainstem that propagate vomiting are located in the dorsal vagal complex (DVC) and express CB_1 and CB_2 receptors (Van Sickle et al. 2001, 2005; Mackie 2005). Enzymes of endocannabinoid synthesis are less abundant in these areas, but enzymes of endocannabinoid degradation, i.e., FAAH and MAGL, have been described in the DVC of the ferret (van Sickle et al. 2001) and the area postrema

of the rat, respectively (Suárez et al. 2010). It is widely known that *Cannabis* and exogenous ligands of CB_1 receptors are able to inhibit vomiting in humans and animal models of emesis (Parker et al. 2011; Izzo and Sharkey 2010). Likewise, anandamide and 2-AG were shown to reduce dose dependently emesis in the ferret (van Sickle et al. 2005). Anandamide, in particular, may play an important part in the control of vomiting by maintaining an "endocannabinoid tone" (Sharkey et al. 2007), a situation pharmacologically created by blockade of FAAH or endocannabinoid transporters, resulting in increased endocannabinoid levels (van Sickle et al. 2005). Thus, the endocannabinoid reuptake inhibitor VDM11 and the FAAH inhibitor URB597 reduced LiCl-induced emesis via CB_1 and CB_2 receptor activation (van Sickle et al. 2005). The MAGL inhibitors JZL184 and MJN110 were both able to reduce emesis in shrews (Parker et al. 2014; Sticht et al. 2012). In humans, in whom motion sickness was induced by parabolic flight maneuvers, sickness was associated with low levels of blood endocannabinoids and reduced expression of CB_1 receptors in leukocytes (Choukèr et al. 2010). In line with this study, dexamethasone prevented motion sickness symptoms in rats partly by increasing anandamide levels in the blood and CB_1 expression in the DVC and the stomach (Zheng et al. 2014).

The mechanisms by which endocannabinoids affect the development of nausea are less clear (reviewed in Rock et al. 2014). Blockade of FAAH, MAGL, or anandamide transporters was shown to reduce gaping reactions to LiCl via CB_1-dependent mechanisms (Cross-Mellor et al. 2007; O'Brien et al. 2013; Parker et al. 2014). Suppression of nausea was also seen after application of 2-AG; however, this effect was not prevented by CB_1 or CB_2 antagonists but was blocked by indomethacin (Sticht et al. 2012). In summary, endocannabinoids are important messengers in the neuronal networks that control vomiting and nausea. Pharmacological manipulation of endocannabinoid degradation may represent a valuable therapeutic approach against emesis.

4.2 Lower Esophageal Sphincter Relaxation

Lower esophageal sphincter (LES) relaxation is the chief mechanism for gastroesophageal reflux. Cannabinoid CB_1 receptor activation, via central and peripheral vagal mechanisms, has been shown to inhibit transient LES relaxations in dogs and ferrets (Lehmann et al. 2002; Partosoedarso et al. 2003; Beaumont et al. 2009), the effect being associated, at least in the dog, with the inhibition of gastroesophageal reflux (Lehmann et al. 2002; Beaumont et al. 2009). Consistent with animal studies, THC (10 and 20 mg) inhibited the increase in transient LES relaxations evoked by meal ingestion and reduced spontaneous swallowing as well as basal LES pressure in healthy volunteers (Beaumont et al. 2009). Intriguingly, the data indicating suppression of transient LES relaxation following CB_1 receptor activation were not confirmed in a subsequent clinical study, in which the CB_1 receptor antagonist rimonabant inhibited the meal-induced increase in transient LES relaxation and increased postprandial LES pressure leading to a lower number of acid reflux events

(Scarpellini et al. 2011). It should be noted, however, that rimonabant may exert potent CB_1-receptor-independent pharmacological effects (Bifulco et al. 2007).

4.3 Gastroprotection

The gastric antisecretory and antiulcer activity of cannabinoids was first observed more than 35 years ago when it was found that THC reduced gastric juice volume and ulcer formation after ligation of the pylorus (Shay rat test) (Sofia et al. 1978). Such early reports have been confirmed by a number of more recent experimental studies showing a decrease in acid production in rodents following CB_1 receptor activation. The site of action is on vagal efferent pathways to the gastric mucosa and not on parietal cells because CB_1 receptor activation results in a reduction in acid secretion induced by 2-deoxy-D-glucose (which increases acid secretion through the release of acetylcholine), but not histamine, which directly activates H_2 receptors on parietal cells (Adami et al. 2002). However, species differences likely exist since cannabinoid receptors have been identified on human parietal cells (Pazos et al. 2008).

In agreement with a gastric antisecretory action, direct or indirect—via FAAH or MAGL inhibition—cannabinoid CB_1 receptor activation results in protective effects in a number of rodent models of gastric ulceration (Dembiński et al. 2006; Naidu et al. 2009; Rutkowska and Fereniec-Gołebiewska 2009; Shujaa et al. 2009; Warzecha et al. 2011; Kinsey et al. 2011). The protective role of endocannabinoids is further supported by the observation that angiotensin II protects gastric mucosa via a mechanism involving CB_1 receptors and 2-AG biosynthesis (Gyires et al. 2014).

4.4 Gastrointestinal Motility

Motility of the gut is regulated by the ENS, which expresses key components of the endocannabinoid system, i.e., cannabinoid receptors, FAAH, and MAGL (Izzo and Sharkey 2010). CB_1 receptor agonists decrease contractility of the stomach, ileum, and colon in rodents and contractility of the ileum and colon in humans through inhibition of acetylcholine release (Aviello et al. 2008; Izzo and Sharkey 2010). In vivo, inhibition of FAAH and MAGL in mouse intestine was shown to lead to increased levels of anandamide and 2-AG, respectively, also resulting in reduced motility (Capasso et al. 2005; Duncan et al. 2008a; Alhouayek et al. 2011). Anandamide seems to play an important role in the regulation of peristaltic reflex pathways within the ENS of rodents (Grider et al. 2009). In contrast to CB_1, the CB_2 receptor may not be involved in the physiological control of gut motility, except in the inflamed gut (Duncan et al. 2008b). Using dronabinol (i.e. THC) in a human study, involvement of CB_1 receptors was shown in gastric accommodation (Ameloot et al. 2010) while small bowel and colonic transit were not influenced by dronabinol (Esfandyari et al. 2006); however, after applying a different dose

regimen of dronabinol, relaxation of the colon and a reduction of postprandial colonic motility and tone were observed (Esfandyari et al. 2007). It also needs to be taken into account that the brain–gut axis may mediate some cannabinoid effects on gut motility because intracerebroventricular activation of cannabinoid receptors by WIN55212-2 slowed down whole gut transit in mice (Izzo et al. 2000; Li et al. 2013). In addition, CB_1 receptor deficiency in the vagal nerves of $Cnr1^{flox/flox}$/Phox2b–Cre mice led to increased gastrointestinal motility in comparison with controls (Vianna et al. 2012).

Endocannabinoids may also be involved in the control of gut motility in experimental inflammatory bowel disease. CB_1 receptor knockout mice displayed disturbed electrophysiological functioning of the colon as compared to their wild-type littermates (Sibaev et al. 2006), while agonism of CB_1 with CP55,940 delayed intestinal hypermotility in murine intestinal inflammation (Izzo et al. 2001). In patients with irritable bowel syndrome (IBS) (with diarrhea and alternating diarrhea), dronabinol inhibited fasting colonic motility but was without effect on sensation and tone (Wong et al. 2011). Endocannabinoids, therefore, control physiological tone and excitability predominantly via CB_1 receptors; however, in pathophysiological disturbances, the endocannabinoid system seems to control only certain aspects of motility, also acting via non-CB_1 targets.

4.5 Intestinal Secretion

Although *Cannabis* preparations have been traditionally used to treat dysentery and diarrhea, only few studies have investigated the effect of cannabinoids on intestinal ion transport and fluid accumulation. Using short-circuit current (Isc) as an indicator of net electrogenic ion transport in Ussing chambers, it was shown that activation of CB_1 receptors may produce an antisecretory effect through a neuronal mechanism involving the inhibition of neurotransmitter(s) release from submucosal plexus neurons and extrinsic primary afferents (Tyler et al. 2000; MacNaughton et al. 2004). In vivo, CB_1 receptor activation reduces intestinal hypersecretion induced by cholera toxin in the mouse small intestine (Izzo et al. 2003).

4.6 Visceral Sensation

Visceral hypersensitivity is a common symptom in gastrointestinal diseases including IBS. There is still a large ongoing debate about the origin of this enhanced visceral perception, with putative causes including altered gas transit, altered gut microbiota composition, alterations in the enterochromaffin cell serotoninergic system, chronic inflammation, and alterations in the gut–brain axis, to name a few (Camilleri et al. 2012; Keszthelyi et al. 2012). Using synthetic agonists it was shown that activation of CB_1 and CB_2 cannabinoid receptors decreases visceral pain in rodent models of colorectal distention (Sanson et al. 2006). It is interesting to note that, upon colon inflammation, the administration of the CB_1 inverse agonist

rimonabant increased hypersensitivity in the same model (Sanson et al. 2006). Similar results were obtained using a model of visceral hypersensitivity induced by stress in rats. Administration of the CB_1 agonist ACEA reduced, while rimonabant increased, the response to colonic distension (Shen et al. 2010). The results obtained with rimonabant in several studies point to a homeostatic role of CB_1 receptors in this context (Sanson et al. 2006; Brusberg et al. 2009; Shen et al. 2010). However, it must be noted that the behavioral response to pain induced by intracolonic instillation of an irritant was reduced by administration of taranabant, another CB_1 inverse agonist (Fichna et al. 2013).

FAAH inhibition was able to reduce visceral pain in models in which stretching movements are monitored following i.p. injection of an irritant. Indeed, administration of FAAH inhibitors reduced the number of stretches, an effect blocked by rimonabant or AM251, thus suggesting the involvement of anandamide and of CB_1 receptors (Haller et al. 2006; Naidu et al. 2009; Fichna et al. 2014). CB_2 receptor antagonism was not able to reverse the analgesic effect of FAAH inhibition (Naidu et al. 2009). Of note, synergy was observed between FAAH inhibition and COX inhibition in this model (Naidu et al. 2009). Further supporting the critical role of anandamide, a recent study demonstrated that this endocannabinoid mediates some effects of serotonin on visceral nociception (Feng et al. 2014).

From a pharmacological standpoint, the antinociceptive effects of FAAH inhibition are of great interest, when compared to CB_1 agonists, as no clear sign of CNS side effects have been reported for FAAH inhibition. However, perhaps mitigating this positive view of cannabinoids in visceral pain is the fact that administration of Δ^9-THC (dronabinol) to healthy volunteers and to IBS patients did not reduce the rectal perception of distension (Esfandyari et al. 2007; Wong et al. 2011; Klooker et al. 2011).

4.7 Intestinal Inflammation

Inflammation of the intestine alters the expression of the cannabinoid receptors and of FAAH and MAGL. However, the changes in expression that are observed are quite different in magnitude and direction depending on the study. Endocannabinoid levels are usually less affected although, again, this depends on the study. For instance, intraperitoneal LPS administration induced an inflammation of the colon and altered cannabinoid receptor expression, but had no effect on 2-AG and NAE levels (Bashashati et al. 2012). Similarly, mustard oil administration did not alter endocannabinoid levels (Fichna et al. 2014). In inflammatory bowel disease (IBD) murine models, 2-AG levels were found to be unchanged (Alhouayek et al. 2011), decreased (Salaga et al. 2014), or increased (Borrelli et al. 2015), whereas AEA was more often increased (D'Argenio et al. 2006; Borrelli et al. 2015). A few studies also analyzed the human inflamed colon during ulcerative colitis (UC) or Crohn's disease (CD), but here again no clear conclusion can be drawn on the variation of endocannabinoid tone (Alhouayek and Muccioli 2012). This is likely due to the inevitable heterogeneity of the samples used in human studies.

Although the impact of inflammation on the endocannabinoid system is highly variable depending on the model and even the study, there is clear evidence supporting the ability of endogenous and exogenous cannabinoids to decrease intestinal inflammation. Indeed, limiting the degradation of NAEs, by inhibiting either FAAH or anandamide uptake, reduces the extent of colitis (D'Argenio et al. 2006; Storr et al. 2008; Salaga et al. 2014). A similar result was also obtained after blocking 2-AG's degradation through inhibition of MAGL (Alhouayek et al. 2011). These positive effects are partly mediated by both cannabinoid receptors as demonstrated using receptor antagonists (Alhouayek et al. 2011). Even though increasing endocannabinoid levels through inhibition of their hydrolysis has proven efficacious, it is important to consider the fact that FAAH controls the levels of numerous bioactive lipids, including in the GI tract (Long et al. 2011; Alhouayek and Muccioli 2014). Therefore, the effects observed upon its inhibition might not only be due to anandamide.

Activation of the cannabinoid receptors remains of course an excellent therapeutic option. This was first shown using nonselective CB_1 and CB_2 agonists (e.g., WIN55212, HU-210) but also using CB_1-selective agonists such as ACEA or CB_2-selective agonists such as JWH-133 (Alhouayek and Muccioli 2012). The efficacy of JWH-133 was shown in numerous IBD models (Singh et al. 2012; Storr et al. 2009; Kimball et al. 2006), further supporting the strategy of selectively activating the CB_2 receptor in the context of colon inflammation and prompting the development of novel CB_2 agonists with anti-inflammatory properties (Tourteau et al. 2013; El Bakali et al. 2012). The CNS side effects associated with CB_1 receptor activation are somewhat hampering the study of centrally active CB_1 agonists in the context of colon inflammation. Once available, peripherally restricted CB_1 receptor agonists should help understand which of the two cannabinoid receptors is the best target for reducing colon inflammation.

4.8 Intestinal Cancer

Cannabinoids are able to suppress proliferation and migration of various cancer cells (Velasco et al. 2012), suggesting an inhibitory role of the endocannabinoid system in tumor growth. In the gut, effects of endocannabinoids on tumor growth and metastasis are mediated primarily via CB_1 receptors (Izzo and Camilleri 2009). Anandamide, for instance, inhibits growth of Caco-2 (Ligresti et al. 2003) and migration of SW480 colon cancer cells via activation of CB_1 receptors (Joseph et al. 2004). Wang et al. (2008) demonstrated that knockout of the *CB1* gene in $Apc^{Min/+}$mice led to increased development of intestinal tumors. Furthermore, in 77 % of tumor samples from colon cancer patients, the *CB1* gene was hypermethylated (Wang et al. 2008). It is generally thought that the aim of an upregulated endocannabinoid system is to restore homeostasis (Schicho and Storr 2010). Accordingly, tumor biopsies from patients with colon cancer revealed increased levels of anandamide and 2-AG, but expression of cannabinoid receptors and FAAH were unchanged in comparison to healthy tissue (Ligresti et al. 2003).

High CB_1 immunoreactivity was described in stage II microsatellite stable colorectal cancer, but correlated with poorer survival rates (Gustafsson et al. 2011), while in another study, CB_1 receptor expression was lower in stage IV than stage I/II or III colon cancer (Jung et al. 2013). However, high *vs* low CB_1 expression in stage IV was associated with poorer survival rate following colorectal surgery (Jung et al. 2013). These observations suggest a more complex expression pattern of CB_1 during cancer disease than previously suspected.

CB_1 activation induces apoptosis in colon cancer cells via inhibition of RAS-MAP kinase and PI3-Akt pathways (Greenhough et al. 2007) or via downregulation of antiapoptotic factors like survivin (Wang et al. 2008). Anandamide inhibited cancer cell proliferation and has been also shown to cause a CB_1-dependent reduction in polyamine levels (Linsalata et al. 2010). In DLD-1 colon cancer cells, some reports describe an involvement of CB_2 receptors in the growth-inhibiting effect of cannabinoids (Ligresti et al. 2003; Romano et al. 2014), partly through TNF-α-induced ceramide synthesis (Cianchi et al. 2008). Interestingly, CB_1 antagonism by rimonabant (Santoro et al. 2009), but not by AM251 (Wang et al. 2008), produced antiproliferative effects in DLD-1 colon cancer cells.

Anandamide induces cannabinoid receptor-independent cell death in apoptosis-resistant colon cancer cells with high levels of COX-2, such as in SW480 cells (Patsos et al. 2005). Since high levels of COX-2 correlate with reduced survival in colorectal cancer patients (Soumaoro et al. 2004), anandamide may be a therapeutic option for apoptosis-resistant colon cancer. An increase in anandamide can be achieved by treatment with FAAH inhibitors, and indeed a study by Izzo et al. (2008) showed that the FAAH inhibitor *N*-arachidonoylserotonin increased colon endocannabinoids and reduced the number of early neoplastic lesions in an azoxymethane-induced colon cancer model. Collectively, endocannabinoids exert anticarcinogenic effects in gastrointestinal cancer through CB_1, CB_2, and CB receptor-independent pathways. In particular, inhibitors of FAAH and probably MAGL (Ye et al. 2011) represent promising future therapeutics for colon cancer.

5 Endocannabinoids and the Urinary Tract

5.1 Cellular Location of Cannabinoid Receptors and Metabolizing Enzymes in the Urinary Tract

In the human bladder, both CB_1 and CB_2 receptors can be localized with immunohistochemistry (IHC) to nerve fibers in the suburothelial region and between smooth muscle bundles (Gratzke et al. 2009; Mukerji et al. 2010; Weinhold et al. 2010; Veress et al. 2013). In biopsies from patients with bladder pain (painful bladder syndrome) or urinary urgency (idiopathic detrusor overactivity), the density of the CB_1 positive nerve fibers is increased (Mukerji et al. 2010). Although there are some inconsistencies in published IHC reports in human urothelium, the majority of findings indicate that both CB_1 and CB_2 receptor staining is higher in the urothelium than the muscle layer (Gratzke et al. 2009;

Tyagi et al. 2009; Mukerji et al. 2010; Weinhold et al. 2010; Bakali et al. 2013). Similar findings pertain to mouse (Hayn et al. 2008; Walczak and Cervero 2011) and rat (Walczak et al. 2009; Veress et al. 2013) bladder. Many of these reports confirmed immunohistochemical results with Western blots (WB) (Gratzke et al. 2009; Tyagi et al. 2009; Bakali et al. 2013; Veress et al. 2013).

FAAH is localized to the urothelium but not the detrusor muscle, using both IHC and WB in the human, rat, and mouse bladder, and FAAH is found to colocalize with CB_2 receptors in human and rat urothelium (Strittmatter et al. 2012). In the mouse bladder, CB_1 receptors colocalize with $P2X_3$ receptors in urothelial cells, primarily the umbrella cells exposed to the bladder lumen, as well as in some nerve fibers mainly in the muscular layer of the bladder wall (Walczak et al. 2009). It is known that with urothelial stretching during bladder filling, umbrella cells release ATP (Wang et al. 2005; Apodaca et al. 2007) which can activate sensory nerves by stimulating P2X receptors. Because most of the CB_1 positive nerve fibers were observed not to co-express $P2X_3$ receptors, any effects of cannabinoids on the purinergic sensory system might be mediated by reduction of urothelial ATP release as opposed to suppression of sensory nerve activity (Walczak et al. 2009). Similar studies in human urothelium of CB_1 and $P2X_3$ receptor colocalization have not been reported. In human bladder, CB_2 receptors and the vesicular acetylcholine transporter (VAChT) colocalize to nerve fibers between strands of detrusor smooth muscle cells. Most of the CB_2 positive nerve fibers and varicosities are observed to also express CGRP. In addition, slender nerve fibers that extended into the urothelium stain positive for both CB_2 and TRPV1 receptors (Gratzke et al. 2009). Because both TRPV1- and CGRP-labeled nerves are associated with sensory function, this co-labeling with CB_2 receptors suggests a possible role for cannabinoids in bladder afferent signaling. CB_1 receptor-positive primary sensory nerve cell bodies are found in the rat dorsal root ganglia (DRG) and spinal cord dorsal horn lamina I and II, subpopulations of which are colocalized with the nociceptive markers CGRP and non-peptidergic *Griffonia* (*Bandeiraea*) *simplicifolia* IB4 isolectin binding (Veress et al. 2013). An immuno-electron microscopic study indicates both a pre- and a postsynaptic localization of CB_1 receptors in dendrites and soma of the rat DRG and dorsal horn (Salio et al. 2002).

5.2 Role of Endocannabinoids in Bladder Function

Electric field stimulation (EFS) of in vitro bladder smooth muscle from all species tested induces transmitter release from intramural nerve endings, thus causing contraction indirectly because blocking sodium channels with tetrodotoxin virtually abolishes EFS-induced contractions. The cannabinoid receptor subtypes involved in these contractions are different in different species. Nerve-evoked (EFS-induced) contractions of in vitro mouse and rat detrusor strips are dose dependently inhibited by cannabinoid agonists (Pertwee and Fernando 1996). In the mouse bladder this is unaffected by the CB_2 antagonist AM630 but reversed by the CB_1 antagonist SR14176A with a potency similar to its K_i for inhibition of [^{3}H]-CP55,940 binding

to CB_1 receptors (Rinaldi-Carmona et al. 1994; Felder et al. 1995). In the rat bladder, both CB_1 and CB_2 antagonists (SR14176A and SR144528, respectively) inhibit with high potency the effects of the non-subtype-selective agonist WIN55212-2 or the CB_2-selective agonist JWH-015 (Martin et al. 2000). This is consistent with an involvement of CB_1 but not CB_2 receptors in the mouse bladder but both CB_1 and CB_2 receptors in the rat bladder. However, nerve-evoked contractions of bladder strips from the dog, pig, primate, or human bladder are completely resistant to activation of cannabinoid receptors with up to 3 μM of the non-subtype-selective full agonist WIN55212-2 (Martin et al. 2000). Based on these findings, the rat and mouse appear to be poor animal models for the effects of cannabinoids in the human bladder at the end-organ level, and any clinical benefit of cannabinoid therapy for human bladder dysfunction is not likely to be mediated by interaction with pre-neuromuscular junction receptors in the bladder wall unless the bladder dysfunction causes induction of bladder pre-junctional cannabinoid receptors.

In the rat urinary bladder, inhibition of FAAH with URB597 reduces the contraction produced by anandamide (Saitoh et al. 2007). The anandamide-induced contraction of the rat bladder is not blocked by CB_1 receptor antagonism with AM251 or CB_2 receptor antagonism with AM630 but virtually abolished by the cyclooxygenase inhibitor indomethacin and partially decreased by the EP1 receptor antagonist ONO9130. Thus, rat bladder anandamide-induced contractions are mediated partly by TRPV1 receptors, partly by increased prostaglandin production and EP1 receptor activation, and perhaps by other yet to be identified mechanisms but not by activation of CB_1 or CB_2 receptors (Saitoh et al. 2007). During filling cystometry in awake rats, intravesical infusion of the central and peripheral FAAH inhibitor oleoyl ethyl amide increases bladder capacity, and this is reversed by the CB_2 antagonist SR144528 but not the CB_1 antagonist rimonabant (Strittmatter et al. 2012). This may indicate that urothelial and suburothelial CB_2 receptors may be the targets for the endocannabinoids that are substrates for FAAH. The FAAH inhibitor URB937 does not readily cross the blood brain barrier since the intravenous IC_{50} for FAAH is 200-fold lower for rat liver than rat brain (Clapper et al. 2010). Intravenous URB937 decreases rat bladder distension-induced afferent nerve activity (both Aδ and C-fibers) in L6 dorsal roots, and this is reversed with either the CB_1 inverse agonist rimonabant or the CB_2 antagonist SR144528 (Aizawa et al. 2014).

The CB_1 agonist ACEA and the CB_2 agonist GP1a reduce nerve-evoked contractions of human bladder muscle strips; however, the paucity of available human tissue precluded quantitative analysis of the data (Tyagi et al. 2009). Results from another laboratory show that anandamide increases but CP55940 decreases nerve-evoked contractions of human, monkey, and rat bladder muscle strips (Gratzke et al. 2009). The anandamide effect in this instance may be a result of its activation of TRPV1 receptors as opposed to its activity at cannabinoid receptors; however, there was no effect of anandamide on baseline tonus of the human, monkey, or rat bladder strips (Gratzke et al. 2009), whereas anandamide was previously reported to induce contraction of rat bladder strips through a CB_1- and CB_2-independent, possibly TRPV1-mediated, mechanism (Saitoh et al. 2007).

The effect of activation of cannabinoid receptors on afferent nerve activity was observed in an ex vivo mouse bladder–nerve preparation in the same investigation (Sect. 5.1) as that in which CB_1 and $P2X_3$ receptors had been found to be colocalized in urothelial umbrella cells (Walczak et al. 2009). Intravesical administration of the CB_1 and CB_2 agonist AZ12646915 reduced the distension-evoked activity of bladder afferents in the pelvic nerve. This inhibition was prevented by previous administration of the CB_1-selective antagonist AM251 implicating CB_1 receptor involvement in the peripheral modulation of bladder afferent signaling. It is not known whether this apparent cannabinoid receptor-mediated suppression of afferent nerve activity induced by bladder distension is actually mediated by $P2X_3$-containing neurons. The mixed CB_1 and CB_2 agonist ajulemic acid has been reported to reduce the increased release of CGRP induced by capsaicin and ATP in the rat bladder. This effect was prevented by the CB_1 antagonist AM251 and the CB_2 antagonist AM630 (Hayn et al. 2008). Because nearly all bladder sensory fibers are immunoreactive for both the capsaicin receptor TRPV1 and CGRP (Avelino et al. 2002), capsaicin-induced CGRP release serves as a marker for measuring bladder afferent sensory nerve activity.

6 OEA and PEA and Their Actions in the Gastrointestinal and Urinary Tract

PEA and OEA are biosynthesized in the gastrointestinal tract, and their levels may change in response to noxious stimuli (Borrelli and Izzo 2009). Pharmacological studies have shown that these two acylethanolamides, particularly PEA, may exert relevant pharmacological effects, both in the gastrointestinal tract and in the urinary tract.

OEA reduces gastric emptying (which represents an important brake against overfilling the gut) and small intestinal transit. The effect of OEA on gastrointestinal motility does not involve PPARα, TRPV1, or cannabinoid receptors (Aviello et al. 2008; Capasso et al. 2005; Cluny et al. 2010). OEA blocked stress-induced accelerated upper GI transit at a dose that had no effect on physiological transit (Cluny et al. 2010), which may be relevant from a therapeutic viewpoint. Preliminary evidence suggests that OEA may exert anti-inflammatory and analgesic actions in the gut. Specifically, OEA reduces intestinal permeability in vitro and exerts—in a PPARα-insensitive way—analgesic properties, reducing the nociceptive responses produced by administration of acetic acid, an experimental model of visceral pain (Suardíaz et al. 2007).

PEA shares the ability of OEA to reduce upper gastrointestinal transit through a cannabinoid receptor-independent-mediated mechanism in physiological states (Capasso et al. 2001, 2005, 2014). In addition, by using a functional experimental model of accelerated transit that models some aspects of post-inflammatory IBS, it has recently been shown that this acylethanolamide normalized functional post-inflammatory accelerated intestinal transit, an effect which involves indirect CB_1 receptor activation and modulation of TRPV1 (Capasso et al. 2014).

Evidence exists that PEA exerts intestinal anti-inflammatory effects. Three independent research groups have recently shown that PEA attenuates murine colitis following intraperitoneal (Esposito et al. 2014; Borrelli et al. 2015; Alhouayek et al. 2015) or oral (Borrelli et al. 2015) administration. Protection can be attained not only by administering PEA exogenously but also by increasing its intestinal levels through *N*-acylethanolamine-hydrolyzing acid amidase (NAAA) inhibition (Alhouayek et al. 2015). The protective effect of oral PEA was associated with changes in TRPV1 channels and GPR55 and CB_1 receptor mRNA expression; was pharmacologically mediated by multiple targets, including CB_2 receptors, GPR55, and PPARα; and was modulated by a TRPV1 channel antagonist (Borrelli et al. 2015). Additionally, PEA (partly via PPARα) has a positive effect on intestinal injury and inflammation caused by ischemia–reperfusion in mice (Di Paola et al. 2012) and reduced (in a mast cell-dependent manner) structural injury, intestinal wall thickness, collagen deposition, and intestinal injury associated with localized, fractionated intestinal irradiation (Wang et al. 2014). In human ulcerative colitis tissues, PEA counteracted enteroglial activation, inhibited macrophage and neutrophil infiltration, and downregulated the expression and release of pro-inflammatory markers (Esposito et al. 2014). Collectively, such results lend support for considering PEA as a new pharmaceutical tool for the treatment of intestinal inflammation, including ulcerative colitis.

PEA has been evaluated for its potential beneficial effects in bladder experimental diseases. Some papers published more than 10 years ago showed that exogenously administered PEA attenuated viscero-visceral hyperreflexia induced by intravesical instillation of nerve growth factor or turpentine (Jaggar et al. 1998; Farquhar-Smith and Rice 2001; Farquhar-Smith et al. 2002). In these models of bladder inflammation, the pharmacological action of PEA was attributed to activation of CB_2-like receptors, since it was counteracted by the selective CB_2 receptor antagonist SR144528. In more recent years, it has been shown that PEA is elevated in experimental models of cystitis induced by cyclophosphamide (Pessina et al. 2015) or acrolein, a cyclophosphamide metabolite (Merriam et al. 2011). More importantly, in the cyclophosphamide model of cystitis, PEA attenuated pain behavior, bladder inflammation, and voiding dysfunction with mechanisms involving CB_1 receptors and PPARα (Pessina et al. 2015).

7 Non-psychotropic Phytocannabinoids and Their Actions in the Gastrointestinal and Urinary Tract

The *Cannabis* plant contains, in addition to THC, non-psychotropic cannabinoids of potential therapeutic interest. These include cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), cannabidivarin (CBDV), and Δ^9-tetrahydrocannabivarin (THCV). Pharmacodynamic studies have shown that such phytocannabinoids may interact with specific targets (e.g., components of the so-called endogenous cannabinoid system, TRP channels) which play a key role in gastrointestinal and urinary diseases.

CBD represents the non-psychotropic phytocannabinoid most thoroughly investigated. CBD restored the increased permeability induced by EDTA or cytokines in a cell culture model of intestinal permeability (Alhamoruni et al. 2010, 2012), counteracted reactive enteric gliosis (De Filippis et al. 2011), induced autophagy in the intestinal epithelium (Koay et al. 2014), reduced the expression of S100B and iNOS proteins in IBD patients' biopsies (De Filippis et al. 2011), and attenuated the ability of IL-17A to elicit mucosal damage in a human colonic explant model (Harvey et al. 2014). In vivo, CBD, given intraperitoneally, was effective in experimental models of colitis (Borrelli et al. 2009; Jamontt et al. 2010) and normalized the hypermotility associated with intestinal inflammation (Capasso et al. 2008). Additionally, intrarectal CBD also has protective effects, suggesting that rectal application of CBD for the therapy of intestinal inflammation may be a practicable option (Schicho and Storr 2012). Finally, CBG and CBC share the ability of CBD to exert anti-inflammatory actions in murine models of colitis (Borrelli et al. 2013; Romano et al. 2013), and CBC also has the ability to reduce motility in the inflamed gut (Izzo et al. 2012).

The link between intestinal inflammation and colon cancer is well established. Consistent with their intestinal anti-inflammatory actions, CBG and CBD have been shown to hamper colon cancer progression in vivo (Aviello et al. 2012; Borrelli et al. 2014; Romano et al. 2014). Results from studies with colorectal carcinoma cells suggest that CBD exerts antiproliferative effects through multiple mechanisms that involve CB_1 receptors, TRPV1, and PPARγ, while CBG inhibits cell growth through TRPM8 antagonism.

Ultimately, CBDV and THCV have been shown to suppress LiCl-induced conditioned gaping, suggesting an anti-nausea potential for these two non-psychotropic phytocannabinoids (Rock et al. 2013). Few studies have investigated the actions of non-psychotropic phytocannabinoids in the urinary tract. Yamada and colleagues showed that CBD induces apoptotic cell death in human T24 bladder cancer cells (Yamada et al. 2010). In addition, CBD has been shown to attenuate acetylcholine receptor-mediated contractility in the rat and human bladder (Capasso et al. 2011), which is consistent with clinical studies showing the ability of Sativex to reduce incontinence episodes in multiple sclerosis patients (Freeman et al. 2006). Sativex is a cannabinoid-based medicine composed primarily of a 1:1 ratio of two *Cannabis sativa* extracts, a *Cannabis sativa* extract with high content of THC and a *Cannabis sativa* extract with high content of CBD. Finally, CBG was found to reduce acetylcholine-induced contractions in the human bladder (Pagano et al. 2015).

8 Potential Therapeutic Applications of Cannabinoids in Gut and Urinary Diseases

Disorders of the gastrointestinal and urinary tract are widespread and costly in terms of health as well as economically. There are extensive unmet medical needs for many conditions where these systems are affected primarily or as a secondary consequence of systemic disease. Experimental evidence suggests that

cannabinoids exert pharmacological actions in the gut potentially beneficial for a number of diseases, including gastrointestinal reflux disease, IBS, IBD, and colon cancer. Notably, preliminary clinical evidence suggests that *Cannabis* use is beneficial for IBD patients (Naftali et al. 2011, 2014; Lal et al. 2011; Ravikoff Allegretti et al. 2013). Cannabinoids are also beneficial in urinary diseases including chronic pelvic pain conditions such as interstitial cystitis and chronic nonbacterial prostatitis, as well as chronic neurological conditions that affect bladder function such as multiple sclerosis and Parkinson's and Alzheimer's diseases. Historically, the major limitation of *Cannabis* was its psychotropic side effects. There are different possible strategies for minimizing these unwanted side effects. First, the on-demand nature of endocannabinoid biosynthesis and degradation could provide a promising approach that would retain the positive effects of cannabinoids in the gut and the bladder. Evidence suggests that increasing endogenous cannabinoid tone, by using FAAH, MAGL, or NAAA inhibitors, results in beneficial effects in the gut (Storr et al. 2008; Alhouayek et al. 2011, 2015) and in the bladder (Merriam et al. 2011). A second strategy would be to selectively target the CB_2 receptors. This strategy is supported by experimental studies showing the ability of selective CB_2 receptor agonists to attenuate experimental intestinal inflammation (Storr et al. 2009), cancer (Cianchi et al. 2008), as well as experimental cystitis (Wang et al. 2013) or bladder emptying in animals with partial urethral obstruction (Gratzke et al. 2011). A third strategy would be to focus on the pharmacological actions of *N*-acylethanolamines, particularly PEA, which are devoid of central psychotropic effects. Apart from being a lipid mediator co-released with anandamide from membrane phospholipids, PEA is a safe plant-derived compound presently marketed as a food component for special medical purposes to alleviate bowel or bladder complaints. Notably, PEA exerts potent anti-inflammatory effects in the gut when given orally (Borrelli et al. 2015) and exerts anti-inflammatory and analgesic actions in experimental models of cystitis (Pessina et al. 2015). Finally, animal studies have clearly shown that non-psychotropic cannabinoids exert beneficial effects in experimental models of inflammatory bowel disease (Borrelli et al. 2009; Romano et al. 2013) and colon cancer (Aviello et al. 2012; Romano et al. 2014). In view of their safety records, such compounds appear to be promising therapeutic agents, at least for the digestive tract.

9 Conclusions and Future Directions

The studies outlined in this review clearly support the notion that the endogenous cannabinoid system is a potentially valuable therapeutic target for gastrointestinal and urinary diseases. However, there are still many questions to be answered. For example, endocannabinoids are metabolized by a large number of different enzymes and, once biosynthesized, act on targets which are not limited to cannabinoid receptors. Establishing the precise role of these enzymes and targets, such as GPR55, constitutes an important objective for future research, especially since some of the enzymes involved in endocannabinoid metabolism, such as the serine hydrolase ABHD6, which is involved in 2-AG degradation, have been largely

unexplored. Another direction for future research is the evaluation of the efficacy of cannabinoids compared to available therapies, a field that has so far generated few published findings. We propose that the potential of the endogenous cannabinoid system warrants further investment for the development of new therapeutic agents for the treatment of gastrointestinal and urinary disease.

References

Adami M, Frati P, Bertini S et al (2002) Gastric antisecretory role and immunohistochemical localization of cannabinoid receptors in the rat stomach. Br J Pharmacol 135:598–606

Aizawa N, Hedlund P, Fullhase C et al (2014) Inhibition of peripheral FAAH depresses activities of bladder mechanosensitive nerve fibers of the rat. J Urol 192:956–963

Alhamoruni A, Lee AC, Wright KL et al (2010) Pharmacological effects of cannabinoids on the Caco-2 cell culture model of intestinal permeability. J Pharmacol Exp Ther 335:92–102

Alhamoruni A, Wright KL, Larvin M et al (2012) Cannabinoids mediate opposing effects on inflammation-induced intestinal permeability. Br J Pharmacol 165:2598–2610

Alhouayek M, Muccioli GG (2012) The endocannabinoid system in inflammatory bowel diseases: from pathophysiology to therapeutic opportunity. Trends Mol Med 18:615–625

Alhouayek M, Muccioli GG (2014) Harnessing the anti-inflammatory potential of palmitoylethanolamide. Drug Discov Today 19:1632–1639

Alhouayek M, Lambert DM, Delzenne NM et al (2011) Increasing endogenous 2-arachidonoylglycerol levels counteracts colitis and related systemic inflammation. FASEB J 25:2711–2721

Alhouayek M, Bottemanne P, Subramanian KV et al (2015) N-acylethanolamine hydrolyzing acid amidase inhibition increases colon PEA levels and counteracts murine colitis. FASEB J 29 (2):650–661

Ameloot K, Janssen P, Scarpellini E et al (2010) Endocannabinoid control of gastric sensorimotor function in man. Aliment Pharmacol Ther 31:1123–1131

Apodaca G, Balestreire E, Birder LA (2007) The uroepithelial-associated sensory web. Kidney Int 72:1057–1064

Avelino A, Cruz C, Nagy I et al (2002) Vanilloid receptor 1 expression in the rat urinary tract. Neuroscience 109:787–798

Aviello G, Romano B, Izzo AA (2008) Cannabinoids and gastrointestinal motility: animal and human studies. Eur Rev Med Pharmacol Sci 12(Suppl 1):81–93

Aviello G, Romano B, Borrelli F et al (2012) Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer. J Mol Med 90:925–934

Bakali E, Elliott RA, Taylor AH et al (2013) Distribution and function of the endocannabinoid system in the rat and human bladder. Int Urogynecol J Pelvic Floor Dysfunct 24:855–863

Bashashati M, Storr MA, Nikas SP et al (2012) Inhibiting fatty acid amide hydrolase normalizes endotoxin-induced enhanced gastrointestinal motility in mice. Br J Pharmacol 165:1556–1571

Beaumont H, Jensen J, Carlsson A et al (2009) Effect of delta9-tetrahydrocannabinol, a cannabinoid receptor agonist, on the triggering of transient lower oesophageal sphincter relaxations in dogs and humans. Br J Pharmacol 156:153–162

Bifulco M, Grimaldi C, Gazzerro P et al (2007) Rimonabant: just an antiobesity drug? Current evidence on its pleiotropic effects. Mol Pharmacol 71:1445–1456

Borrelli F, Izzo AA (2009) Role of acylethanolamides in the gastrointestinal tract with special reference to food intake and energy balance. Best Pract Res Clin Endocrinol Metab 23:33–49

Borrelli F, Aviello G, Romano B et al (2009) Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. J Mol Med 87:1111–1121

Borrelli F, Fasolino I, Romano B et al (2013) Beneficial effect of the non-psychotropic plant cannabinoid cannabigerol on experimental inflammatory bowel disease. Biochem Pharmacol 85:1306–1316

Borrelli F, Pagano E, Romano B et al (2014) Colon carcinogenesis is inhibited by the TRPM8 antagonist cannabigerol, a Cannabis-derived non-psychotropic cannabinoid. Carcinogenesis 35(12):2787–2797

Borrelli F, Romano B, Petrosino S et al (2015) Palmitoylethanolamide, a naturally occurring lipid, is an orally effective intestinal anti-inflammatory agent. Br J Pharmacol 172(1):142–158

Brusberg M, Arvidsson S, Kang D et al (2009) CB1 receptors mediate the analgesic effects of cannabinoids on colorectal distension-induced visceral pain in rodents. J Neurosci 29:1554–1564

Camilleri M, Lasch K, Zhou W (2012) Irritable bowel syndrome: methods, mechanisms, and pathophysiology. The confluence of increased permeability, inflammation, and pain in irritable bowel syndrome. Am J Physiol Gastrointest Liver Physiol 303:G775–G785

Capasso R, Izzo AA, Fezza F et al (2001) Inhibitory effect of palmitoylethanolamide on gastrointestinal motility in mice. Br J Pharmacol 134:945–950

Capasso R, Matias I, Lutz B et al (2005) Fatty acid amide hydrolase controls mouse intestinal motility in vivo. Gastroenterology 129:941–951

Capasso R, Borrelli F, Aviello G et al (2008) Cannabidiol, extracted from Cannabis sativa, selectively inhibits inflammatory hypermotility in mice. Br J Pharmacol 154:1001–1008

Capasso R, Aviello G, Borrelli F et al (2011) Inhibitory effect of standardized cannabis sativa extract and its ingredient cannabidiol on rat and human bladder contractility. Urology 77:1006.e9–1006.e15

Capasso R, Orlando P, Pagano E et al (2014) Palmitoylethanolamide normalizes intestinal motility in a model of post-inflammatory accelerated transit: involvement of CB_1 receptors and TRPV1 channels. Br J Pharmacol 171:4026–4037

Casu MA, Porcella A, Ruiu S et al (2003) Differential distribution of functional cannabinoid CB1 receptors in the mouse gastroenteric tract. Eur J Pharmacol 459:97–105

Choukèr A, Kaufmann I, Kreth S et al (2010) Motion sickness, stress and the endocannabinoid system. PLoS One 5, e10752

Cianchi F, Papucci L, Schiavone N et al (2008) Cannabinoid receptor activation induces apoptosis through tumor necrosis factor alpha-mediated ceramide de novo synthesis in colon cancer cells. Clin Cancer Res 14:7691–7700

Clapper JR, Moreno-Sanz G, Russo R et al (2010) Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism. Nat Neurosci 13:1265–1270

Cluny NL, Keenan CM, Duncan M et al (2010) Naphthalen-1-yl-(4-pentyloxynaphthalen-1-yl) methanone (SAB378), a peripherally restricted cannabinoid CB1/CB2 receptor agonist, inhibits gastrointestinal motility but has no effect on experimental colitis in mice. J Pharmacol Exp Ther 334:973–980

Cross-Mellor SK, Ossenkopp KP, Piomelli D et al (2007) Effects of the FAAH inhibitor, URB597, and anandamide on lithium-induced taste reactivity responses: a measure of nausea in the rat. Psychopharmacology 190:135–143

D'Argenio G, Valenti M, Scaglione G et al (2006) Up-regulation of anandamide levels as an endogenous mechanism and a pharmacological strategy to limit colon inflammation. FASEB J 20:568–570

De Filippis D, Esposito G, Cirillo C et al (2011) Cannabidiol reduces intestinal inflammation through the control of neuroimmune axis. PLoS One 6, e28159

De Petrocellis L, Bisogno T, Ligresti A et al (2002) Effect on cancer cell proliferation of palmitoylethanolamide, a fatty acid amide interacting with both the cannabinoid and vanilloid signalling systems. Fundam Clin Pharmacol 16:297–302

Dembiński A, Warzecha Z, Ceranowicz P et al (2006) Cannabinoids in acute gastric damage and pancreatitis. J Physiol Pharmacol 57:137–154

Di Paola R, Impellizzeri D, Torre A et al (2012) Effects of palmitoylethanolamide on intestinal injury and inflammation caused by ischemia-reperfusion in mice. J Leukoc Biol 91:911–920
Duncan M, Mouihate A, Mackie K et al (2008a) Cannabinoid CB2 receptors in the enteric nervous system modulate gastrointestinal contractility in lipopolysaccharide-treated rats. Am J Physiol Gastrointest Liver Physiol 295:G78–G87
Duncan M, Thomas AD, Cluny NL et al (2008b) Distribution and function of monoacylglycerol lipase in the gastrointestinal tract. Am J Physiol Gastrointest Liver Physiol 295:G1255–G1265
El Bakali J, Gilleron P, Body-Malapel M et al (2012) 4-Oxo-1,4-dihydropyridines as selective CB (2) cannabinoid receptor ligands. Part 2: discovery of new agonists endowed with protective effect against experimental colitis. J Med Chem 55:8948–8952
Esfandyari T, Camilleri M, Ferber I et al (2006) Effect of a cannabinoid agonist on gastrointestinal transit and postprandial satiation in healthy human subjects: a randomized, placebo-controlled study. Neurogastroenterol Motil 18:831–838
Esfandyari T, Camilleri M, Busciglio I et al (2007) Effects of a cannabinoid receptor agonist on colonic motor and sensory functions in humans: a randomized, placebo-controlled study. Am J Physiol Gastrointest Liver Physiol 293:G137–G145
Esposito G, Capoccia E, Turco F et al (2014) Palmitoylethanolamide improves colon inflammation through an enteric glia/toll like receptor 4-dependent PPAR-alpha activation. Gut 63:1300–1312
Farquhar-Smith WP, Rice AS (2001) Administration of endocannabinoids prevents a referred hyperalgesia associated with inflammation of the urinary bladder. Anesthesiology 94:507–513
Farquhar-Smith WP, Jaggar SI, Rice AS (2002) Attenuation of nerve growth factor-induced visceral hyperalgesia via cannabinoid CB(1) and CB(2)-like receptors. Pain 97:11–21
Felder CC, Joyce KE, Briley EM et al (1995) Comparison of the pharmacology and signal transduction of the human cannabinoid CB1 and CB2 receptors. Mol Pharmacol 48:443–450
Feng CC, Yan XJ, Chen X et al (2014) Vagal anandamide signaling via cannabinoid receptor 1 contributes to luminal 5-HT modulation of visceral nociception in rats. Pain 155:1591–1604
Fichna J, Sibaev A, Salaga M et al (2013) The cannabinoid-1 receptor inverse agonist taranabant reduces abdominal pain and increases intestinal transit in mice. Neurogastroenterol Motil 25: e550–e559
Fichna J, Salaga M, Stuart J et al (2014) Selective inhibition of FAAH produces antidiarrheal and antinociceptive effect mediated by endocannabinoids and cannabinoid-like fatty acid amides. Neurogastroenterol Motil 26:470–481
Freeman RM, Adekanmi O, Waterfield MR et al (2006) The effect of cannabis on urge incontinence in patients with multiple sclerosis: a multicentre, randomised placebo-controlled trial (CAMS-LUTS). Int Urogynecol J Pelvic Floor Dysfunct 17:636–641
Fu J, Gaetani S, Oveisi F et al (2003) Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. Nature 425:90–93
Gratzke C, Streng T, Park A et al (2009) Distribution and function of cannabinoid receptors 1 and 2 in the rat, monkey and human bladder. J Urol 181:1939–1948
Gratzke C, Streng T, Stief CG et al (2011) Cannabinor, a selective cannabinoid-2 receptor agonist, improves bladder emptying in rats with partial urethral obstruction. J Urol 185:731–736
Greenhough A, Patsos HA, Williams AC et al (2007) The cannabinoid Δ9-tetrahydrocannabinol inhibits RAS-MAPK and PI3K-AKT survival signalling and induces BAD-mediated apoptosis in colorectal cancer cells. Int J Cancer 121:2172–2180
Grider JR, Mahavadi S, Li Y et al (2009) Modulation of motor and sensory pathways of the peristaltic reflex by cannabinoids. Am J Physiol Gastrointest Liver Physiol 297:G539–G549
Grinspoon L, Bakalar JB (1995) Marihuana as medicine. A plea for reconsideration. JAMA 273:1875–1876
Gustafsson SB, Palmqvist R, Henriksson ML et al (2011) High tumour cannabinoid CB1 receptor immunoreactivity negatively impacts disease-specific survival in stage II microsatellite stable colorectal cancer. PLoS One 6, e23003

Gyires K, Rónai AZ, Zádori ZS et al (2014) Angiotensin II-induced activation of central AT1 receptors exerts endocannabinoid-mediated gastroprotective effect in rats. Mol Cell Endocrinol 382:971–978

Haller VL, Cichewicz DL, Welch SP (2006) Non-cannabinoid CB1, non-cannabinoid CB2 antinociceptive effects of several novel compounds in the PPQ stretch test in mice. Eur J Pharmacol 546:60–68

Harvey BS, Sia TC, Wattchow DA et al (2014) Interleukin 17A evoked mucosal damage is attenuated by cannabidiol and anandamide in a human colonic explant model. Cytokine 65:236–244

Hayn MH, Ballesteros I, de Miguel F et al (2008) Functional and immunohistochemical characterization of CB1 and CB2 receptors in rat bladder. Urology 72:1174–1178

Izzo AA, Camilleri M (2009) Cannabinoids in intestinal inflammation and cancer. Pharmacol Res 60:117–125

Izzo AA, Sharkey KA (2010) Cannabinoids and the gut: new developments and emerging concepts. Pharmacol Ther 126:21–38

Izzo AA, Pinto L, Borrelli F et al (2000) Central and peripheral cannabinoid modulation of gastrointestinal transit in physiological states or during the diarrhoea induced by croton oil. Br J Pharmacol 129:1627–1632

Izzo AA, Fezza F, Capasso R et al (2001) Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. Br J Pharmacol 134:563–570

Izzo AA, Capasso F, Costagliola A et al (2003) An endogenous cannabinoid tone attenuates cholera toxin-induced fluid accumulation in mice. Gastroenterology 125:765–774

Izzo AA, Aviello G, Petrosino S et al (2008) Increased endocannabinoid levels reduce the development of precancerous lesions in the mouse colon. J Mol Med 86:89–98

Izzo AA, Capasso R, Aviello G et al (2012) Inhibitory effect of cannabichromene, a major non-psychotropic cannabinoid extracted from Cannabis sativa, on inflammation-induced hypermotility in mice. Br J Pharmacol 166:1444–1460

Jaggar SI, Hasnie FS, Sellaturay S et al (1998) The anti-hyperalgesic actions of the cannabinoid anandamide and the putative CB2 receptor agonist palmitoylethanolamide in visceral and somatic inflammatory pain. Pain 76:189–199

Jamontt JM, Molleman A, Pertwee RG et al (2010) The effects of Delta-tetrahydrocannabinol and cannabidiol alone and in combination on damage, inflammation and in vitro motility disturbances in rat colitis. Br J of Pharmacol 160:712–723

Joseph J, Niggemann B, Zaenker KS et al (2004) Anandamide is an endogenous inhibitor for the migration of tumor cells and T lymphocytes. Cancer Immunol Immunother 53:723–728

Jung CK, Kang WK, Park JM et al (2013) Expression of the cannabinoid type I receptor and prognosis following surgery in colorectal cancer. Oncol Lett 5:870–876

Keszthelyi D, Troost FJ, Simren M et al (2012) Revisiting concepts of visceral nociception in irritable bowel syndrome. Eur J Pain 16:1444–1454

Kimball ES, Schneider CR, Wallace NH et al (2006) Agonists of cannabinoid receptor 1 and 2 inhibit experimental colitis induced by oil of mustard and by dextran sulfate sodium. Am J Physiol 291:G364–G371

Kinsey SG, Nomura DK, O'Neal ST et al (2011) Inhibition of monoacylglycerol lipase attenuates nonsteroidal anti-inflammatory drug-induced gastric hemorrhages in mice. J Pharmacol Exp Ther 338:795–802

Klooker TK, Leliefeld KE, Van Den Wijngaard RM et al (2011) The cannabinoid receptor agonist delta-9-tetrahydrocannabinol does not affect visceral sensitivity to rectal distension in healthy volunteers and IBS patients. Neurogastroenterol Motil 23:30–35

Koay LC, Rigby RJ, Wright KL (2014) Cannabinoid-induced autophagy regulates suppressor of cytokine signaling-3 in intestinal epithelium. Am J Physiol Gastrointest Liver Physiol 307: G140–G148

Lal S, Prasad N, Ryan M et al (2011) Cannabis use amongst patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol 23:891–896
Lehmann A, Blackshaw LA, Brändén L (2002) Cannabinoid receptor agonism inhibits transient lower esophageal sphincter relaxations and reflux in dogs. Gastroenterology 123:1129–1134
Li K, Fichna J, Schicho R et al (2013) A role for O-1602 and G protein-coupled receptor GPR55 in the control of colonic motility in mice. Neuropharmacology 71:255–263
Ligresti A, Bisogno T, Matias I et al (2003) Possible endocannabinoid control of colorectal cancer growth. Gastroenterology 125:677–687
Linsalata M, Notarnicola M, Tutino V et al (2010) Effects of anandamide on polyamine levels and cell growth in human colon cancer cells. Anticancer Res 30:2583–2589
Long JZ, LaCava M, Jin X et al (2011) An anatomical and temporal portrait of physiological substrates for fatty acid amide hydrolase. J Lipid Res 52:337–344
Mackie K (2005) Distribution of cannabinoid receptors in the central and peripheral nervous system. Handb Exp Pharmacol 168:299–325
MacNaughton WK, Van Sickle MD, Keenan CM et al (2004) Distribution and function of the cannabinoid-1 receptor in the modulation of ion transport in the guinea pig ileum: relationship to capsaicin-sensitive nerves. Am J Physiol Gastrointest Liver Physiol 286:G863–G871
Martin RS, Luong LA, Welsh NJ et al (2000) Effects of cannabinoid receptor agonists on neuronally-evoked contractions of urinary bladder tissues isolated from rat, mouse, pig, dog, monkey and human. Br J Pharmacol 129:1707–1715
Merriam FV, Wang ZY, Hillard CJ et al (2011) Inhibition of fatty acid amide hydrolase suppresses referred hyperalgesia induced by bladder inflammation. BJU Int 108:1145–1149
Muccioli GG (2010) Endocannabinoid biosynthesis and inactivation, from simple to complex. Drug Discov Today 15:474–483
Mukerji G, Yiangou Y, Agarwal SK et al (2010) Increased cannabinoid receptor 1-immunoreactive nerve fibers in overactive and painful bladder disorders and their correlation with symptoms. Urology 75(6):1514.e1515–1514.e1520
Naftali T, Lev LB, Yablecovitch D, Half E et al (2011) Treatment of Crohn's disease with cannabis: an observational study. Isr Med Assoc J 13:455–458
Naftali T, Mechulam R, Lev LB et al (2014) Cannabis for inflammatory bowel disease. Dig Dis 32:468–474
Naidu PS, Booker L, Cravatt BF et al (2009) Synergy between enzyme inhibitors of fatty acid amide hydrolase and cyclooxygenase in visceral nociception. J Pharmacol Exp Ther 329:48–56
Nocerino E, Amato M, Izzo AA (2000) Cannabis and cannabinoid receptors. Fitoterapia 71(Suppl 1):S6–S12
O'Brien LD, Limebeer CL, Rock EM et al (2013) Anandamide transport inhibition by ARN272 attenuates nausea-induced behaviour in rats, and vomiting in shrews (Suncus murinus). Br J Pharmacol 170:1130–1136
Overton HA, Babbs AJ, Doel SM et al (2006) Deorphanization of a G protein-coupled receptor for oleoylethanolamide and its use in the discovery of small-molecule hypophagic agents. Cell Metab 3:167–175
Pagano E, Montanaro V, Di Girolamo A et al (2015) Effect of non-psychotropic plant-derived cannabinoids on bladder contractility: focus on cannabigerol. Nat Prod Commun 10:1009–1012
Parker LA, Rock EM, Limebeer CL (2011) Regulation of nausea and vomiting by cannabinoids. Br J Pharmacol 163:1411–1422
Parker LA, Niphakis MJ, Downey R et al (2014) Effect of selective inhibition of monoacylglycerol lipase (MAGL) on acute nausea, anticipatory nausea, and vomiting in rats and Suncus murinus. Psychopharmacology 232:583–93
Partosoedarso ER, Abrahams TP, Scullion RT et al (2003) Cannabinoid1 receptor in the dorsal vagal complex modulates lower oesophageal sphincter relaxation in ferrets. J Physiol 550:149–158

Patsos HA, Hicks DJ, Dobson RR et al (2005) The endogenous cannabinoid, anandamide, induces cell death in colorectal carcinoma cells: a possible role for cyclooxygenase 2. Gut 54:1741–1750

Pazos MR, Tolón RM, Benito C et al (2008) Cannabinoid CB1 receptors are expressed by parietal cells of the human gastric mucosa. J Histochem Cytochem 56:511–516

Pertwee RG, Fernando SR (1996) Evidence for the presence of cannabinoid CB1 receptors in mouse urinary bladder. Br J Pharmacol 118:2053–2058

Pessina F, Capasso R, Borrelli F et al (2015) Protective effect of palmitoylethanolamide, a naturally-occurring molecule, in a rat model of cystitis. J Urol 193(4):1401–1408

Ravikoff Allegretti J, Courtwright A, Lucci M et al (2013) Marijuana use patterns among patients with inflammatory bowel disease. Inflamm Bowel Dis 19:2809–2814

Rinaldi-Carmona M, Barth F, Heaulme M et al (1994) SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 350:240–244

Rock EM, Sticht MA, Duncan M et al (2013) Evaluation of the potential of the phytocannabinoids, cannabidivarin (CBDV) and Δ(9)—tetrahydrocannabivarin (THCV), to produce CB1 receptor inverse agonism symptoms of nausea in rats. Br J Pharmacol 170:671–678

Rock EM, Limebeer CL, Parker LA (2014) Anticipatory nausea in animal models: a review of potential novel therapeutic treatments. Exp Brain Res 232:2511–2534

Romano B, Borrelli F, Fasolino I et al (2013) The cannabinoid TRPA1 agonist cannabichromene inhibits nitric oxide production in macrophages and ameliorates murine colitis. Br J Pharmacol 169:213–229

Romano B, Borrelli F, Pagano E et al (2014) Inhibition of colon carcinogenesis by a standardized Cannabis sativa extract with high content of cannabidiol. Phytomedicine 21:631–639

Rutkowska M, Fereniec-Gołebiewska L (2009) Involvement of nitric oxide in the gastroprotective effect of ACEA, a selective cannabinoid CB1 receptor agonist, on aspirin-induced gastric ulceration. Pharmazie 64:595–597

Saitoh C, Kitada C, Uchida W et al (2007) The differential contractile responses to capsaicin and anandamide in muscle strips isolated from the rat urinary bladder. Eur J Pharmacol 570:182–187

Salaga M, Mokrowiecka A, Zakrzewski PK et al (2014) Experimental colitis in mice is attenuated by changes in the levels of endocannabinoid metabolites induced by selective inhibition of fatty acid amide hydrolase (FAAH). J Crohns Colitis 8:998–1009

Salio C, Fischer J, Franzoni MF et al (2002) Pre- and postsynaptic localizations of the CB1 cannabinoid receptor in the dorsal horn of the rat spinal cord. Neuroscience 110:755–764

Sanson M, Bueno L, Fioramonti J (2006) Involvement of cannabinoid receptors in inflammatory hypersensitivity to colonic distension in rats. Neurogastroenterol Motil 18:949–956

Santoro A, Pisanti S, Grimaldi C et al (2009) Rimonabant inhibits human colon cancer cell growth and reduces the formation of precancerous lesions in the mouse colon. Int J Cancer 125:996–1003

Scarpellini E, Blondeau K, Boecxstaens V (2011) Effect of rimonabant on oesophageal motor function in man. Aliment Pharmcol Ther 33:730–737

Schicho R, Storr M (2010) Targeting the endocannabinoid system for gastrointestinal diseases: future therapeutic strategies. Expert Rev Clin Pharmacol 3:193–207

Schicho R, Storr M (2012) Topical and systemic cannabidiol improves trinitrobenzene sulfonic acid colitis in mice. Pharmacology 89:149–155

Sharkey KA, Cristino L, Oland LD et al (2007) Arvanil, anandamide and N-arachidonoyl-dopamine (NADA) inhibit emesis through cannabinoid CB1 and vanilloid TRPV1 receptors in the ferret. Eur J Neurosci 25:2773–2782

Sharkey KA, Darmani NA, Parker LA (2014) Regulation of nausea and vomiting by cannabinoids and the endocannabinoid system. Eur J Pharmacol 722:134–146

Shen L, Yang XJ, Qian W et al (2010) The role of peripheral cannabinoid receptors type 1 in rats with visceral hypersensitivity induced by chronic restraint stress. J Neurogastroenterol Motil 16:281–290

Shujaa N, Zadori ZS, Ronai AZ et al (2009) Analysis of the effect of neuropeptides and cannabinoids in gastric mucosal defense initiated centrally in the rat. J Physiol Pharmacol 60:93–100
Sibaev A, Massa F, Yüce B et al (2006) CB1 and TRPV1 receptors mediate protective effects on colonic electrophysiological properties in mice. J Mol Med 84:513–520
Singh UP, Singh NP, Singh B et al (2012) Cannabinoid receptor-2 (CB2) agonist ameliorates colitis in IL-10(-/-) mice by attenuating the activation of T cells and promoting their apoptosis. Toxicol Appl Pharmacol 258:256–267
Sofia RD, Diamantis W, Edelson J (1978) Effect of delta9-tetrahydrocannabinol on the gastrointestinal tract of the rat. Pharmacology 17:79–82
Soumaoro LT, Uetake H, Higuchi T et al (2004) Cyclooxygenase-2 expression: a significant prognostic indicator for patients with colorectal cancer. Clin Cancer Res 10:8465–8471
Sticht MA, Long JZ, Rock EM et al (2012) Inhibition of monoacylglycerol lipase attenuates vomiting in Suncus murinus and 2-arachidonoyl glycerol attenuates nausea in rats. Br J Pharmacol 165:2425–2435
Storr MA, Keenan CM, Emmerdinger D (2008) Targeting endocannabinoid degradation protects against experimental colitis in mice: involvement of CB1 and CB2 receptors. J Mol Med 86:925–936
Storr MA, Keenan CM, Zhang H et al (2009) Activation of the cannabinoid 2 receptor (CB2) protects against experimental colitis. Inflamm Bowel Dis 15:1678–1685
Strittmatter F, Gandaglia G, Benigni F et al (2012) Expression of fatty acid amide hydrolase (FAAH) in human, mouse, and rat urinary bladder and effects of FAAH inhibition on bladder function in awake rats. Eur Urol 61:98–106
Suardíaz M, Estivill-Torrús G, Goicoechea C et al (2007) Analgesic properties of oleoylethanolamide (OEA) in visceral and inflammatory pain. Pain 133:99–110
Suárez J, Romero-Zerbo SY, Rivera P et al (2010) Endocannabinoid system in the adult rat circumventricular areas: an immunohistochemical study. J Comp Neurol 518:3065–3085
Tourteau A, Andrzejak V, Body-Malapel M et al (2013) 3-Carboxamido-5-aryl-isoxazoles as new CB2 agonists for the treatment of colitis. Bioorg Med Chem 21:5383–5394
Tyagi V, Philips BJ, Su R et al (2009) Differential expression of functional cannabinoid receptors in human bladder detrusor and urothelium. J Urol 181:1932–1938
Tyler K, Hillard CJ, Greenwood-Van Meerveld B (2000) Inhibition of small intestinal secretion by cannabinoids is CB1 receptor-mediated in rats. Eur J Pharmacol 409:207–211
Van Sickle MD, Oland LD, Ho W et al (2001) Cannabinoids inhibit emesis through CB1 receptors in the brainstem of the ferret. Gastroenterology 121:767–774
Van Sickle MD, Duncan M, Kingsley PJ et al (2005) Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 310:329–332
Velasco G, Sánchez C, Guzmán M (2012) Towards the use of cannabinoids as antitumour agents. Nat Rev Cancer 12:436–444
Veress G, Meszar Z, Muszil D et al (2013) Characterisation of cannabinoid 1 receptor expression in the perikarya, and peripheral and spinal processes of primary sensory neurons. Brain Struct Funct 218:733–750
Vianna CR, Donato J Jr, Rossi J et al (2012) Cannabinoid receptor 1 in the vagus nerve is dispensable for body weight homeostasis but required for normal gastrointestinal motility. J Neurosci 32:10331–10337
Walczak JS, Cervero F (2011) Local activation of cannabinoid CB1 receptors in the urinary bladder reduces the inflammation-induced sensitization of bladder afferents. Mol Pain 7:31
Walczak JS, Price TJ, Cervero F (2009) Cannabinoid CB1 receptors are expressed in the mouse urinary bladder and their activation modulates afferent bladder activity. Neuroscience 159:1154–1163
Wang EC, Lee JM, Ruiz WG et al (2005) ATP and purinergic receptor-dependent membrane traffic in bladder umbrella cells. J Clin Invest 115:2412–2422

Wang D, Wang H, Ning W et al (2008) Loss of cannabinoid receptor 1 accelerates intestinal tumor growth. Cancer Res 68:6468–6476

Wang ZY, Wang P, Bjorling DE (2013) Activation of cannabinoid receptor 2 inhibits experimental cystitis. Am J Physiol Regul Integr Comp Physiol 304:R846–R853

Wang J, Zheng J, Kulkarni A et al (2014) Palmitoylethanolamide regulates development of intestinal radiation injury in a mast cell-dependent manner. Dig Dis Sci 59:2693–2703

Warzecha Z, Dembinski A, Ceranowicz P (2011) Role of sensory nerves in gastroprotective effect of anandamide in rats. J Physiol Pharmacol 62:207–217

Weinhold P, Gratzke C, Streng T et al (2010) TRPA1 receptor induced relaxation of the human urethra involves TRPV1 and cannabinoid receptor mediated signals, and cyclooxygenase activation. J Urol 183:2070–2076

Wong BS, Camilleri M, Busciglio I et al (2011) Pharmacogenetic trial of a cannabinoid agonist shows reduced fasting colonic motility in patients with nonconstipated irritable bowel syndrome. Gastroenterology 141:1638–1647.e1–1638–1647.e7

Wright K, Rooney N, Feeney M et al (2005) Differential expression of cannabinoid receptors in the human colon: cannabinoids promote epithelial wound healing. Gastroenterology 129:437–453

Yamada T, Ueda T, Shibata Y et al (2010) TRPV2 activation induces apoptotic cell death in human T24 bladder cancer cells: a potential therapeutic target for bladder cancer. Urology 76:509.e1–509.e7

Ye L, Zhang B, Seviour EG et al (2011) Monoacylglycerol lipase (MAGL) knockdown inhibits tumor cells growth in colorectal cancer. Cancer Lett 307:6–17

Zheng Y, Wang XL, Mo FF et al (2014) Dexamethasone alleviates motion sickness in rats in part by enhancing the endocannabinoid system. Eur J Pharmacol 727:99–105