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Endocannabinoids in the gastrointestinal tract

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Lee Y, Jo J, Chung HY, Pothoulakis C, Im E. Endocannabinoids in the gastrointestinal tract. *Am J Physiol Gastrointest Liver Physiol* 311: G655–G666, 2016. First published August 18, 2016; doi:10.1152/ajpgi.00294.2015.—The endocannabinoid system mainly consists of endogenously produced cannabinoids (endocannabinoids) and two G protein-coupled receptors (GPCRs), cannabinoid receptors 1 and 2 (CB_1 and CB_2). This system also includes enzymes responsible for the synthesis and degradation of endocannabinoids and molecules required for the uptake and transport of endocannabinoids. In addition, endocannabinoid-related lipid mediators and other putative endocannabinoid receptors, such as transient receptor potential channels and other GPCRs, have been identified. Accumulating evidence indicates that the endocannabinoid system is a key modulator of gastrointestinal physiology, influencing satiety, emesis, immune function, mucosal integrity, motility, secretion, and visceral sensation. In light of therapeutic benefits of herbal and synthetic cannabinoids, the vast potential of the endocannabinoid system for the treatment of gastrointestinal diseases has been demonstrated. This review focuses on the role of the endocannabinoid system in gut homeostasis and in the pathogenesis of intestinal disorders associated with intestinal motility, inflammation, and cancer. Finally, links between gut microorganisms and the endocannabinoid system are briefly discussed.

endocannabinoid; cannabinoid receptor; intestine; inflammation; cancer

THE PLANT *CANNABIS* HAS BEEN used for millennia to treat a wide range of human illnesses as evidenced by medicinal reports issued in China and India. The main active compound of *Cannabis sativa*, Δ^9-tetrahydrocannabinol (Δ^9-THC), was identified and characterized in 1964 (84). Subsequently, more than 80 phytocannabinoids were identified and various active analogs with different potencies were synthesized (56). Specific membrane-bound endogenous cannabinoid receptors were discovered about 20 years later after the identification of Δ^9-THC; the first receptor was found in 1988 and the second receptor in 1993 (30, 90). These discoveries led to rapid advancements in the understanding of the endocannabinoid system and in the developments of new therapies for many human diseases (56). In particular, it has become evident that the endocannabinoid system plays an important role in gastrointestinal pathophysiology and that cannabinoid-based drugs may be of therapeutic value in this context. In this review, we define the endocannabinoid system and discuss novel findings demonstrating that this system influences a variety of intestinal disorders and also acts as a liaison between the gut microbiota and the host.

The Endocannabinoid System

Endocannabinoids. Endogenous agonists of cannabinoid receptors are called "endocannabinoids" and are produced in humans and animals. An extended list of endocannabinoids includes *N*-arachidonoylethanolamine (anandamide, AEA), 2-arachidonoylglycerol (2-AG), 2-arachidonyl glyceryl ether (noladin ether), *N*-arachidonoyl dopamine (NADA), and *O*-arachidonoyl-ethanolamine (virodhamine) (31). The most widely studied endocannabinoids are AEA and 2-AG. AEA was the first endocannabinoid identified in porcine brain and is a member of the *N*-acylethanolamine (NAE) family (30), whereas 2-AG is a monoacylglycerol and was first isolated from rat brain and canine gut (82, 127). Noladin ether was first synthesized as an analog of 2-AG but later isolated from porcine brain (51, 83). In addition, endocannabinoid analogs that structurally resemble prototypic endocannabinoids either enhance the effects of endocannabinoids or exert their own activities (17). Those analogs include other NAEs, such as *N*-linoleylethanolamine (LEA), *N*-oleoylethanolamine (OEA), *N*-palmitoylethanolamine (PEA), and *N*-stearoylethanolamine (SEA), and AG family lipids, such as palmitoylglycerol (2-PG) and oleoylglycerol (2-OG). Research on the endocannabinoid system remains active and other endocannabinoid-related lipid mediators are continuously identified, and these studies raise a wide spectrum of questions about the diverse physiological and pathological roles of endocannabinoids.

Synthesis and degradation pathways of endocannabinoids. Endocannabinoids are synthesized on demand from membrane lipid precursors, unlike other classical peptide transmitters, which in general are stored in vesicles and released in response to various stimuli (41, 101). Calcium influx into postsynaptic cells initiates the biosynthesis of endocannabinoids (45) (Fig.

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1). For AEA, biosynthesis begins with the activation of *N*-acyltransferase (NAT), which converts the membrane lipid phosphatidylethanolamine (PE) to *N*-acylphosphatidylethanolamine (NAPE). Sequentially, NAPE-phospholipase D (NAPE-PLD) catalyzes NAPE and produces AEA (34, 87). Moreover, AEA can be synthesized through alternative pathways involving the hydrolysis of NAPEs by α-β-hydrolase domain-containing protein 4 (ABHD4), glycerophosphodiester phosphodiesterase 1, phospholipase C (PLC), or tyrosine-protein phosphatase nonreceptor type 22 (132). The biosynthesis of 2-AG begins with the PLC-mediated hydrolysis of the membrane lipid, phosphatidylinositol (PI) to produce diacylglycerol (DAG), which is subsequently converted to 2-AG by diacylglycerol lipases (DAGL) α and β (33). After being released into the extracellular space, endocannabinoids bind to cannabinoid receptors and exert their biological activities. Conversely, to terminate their effects, endocannabinoids are removed from the extracellular space by membrane transporters and degraded by catalytic enzymes (45). AEA is degraded into arachidonic acid (AA) and ethanolamine by fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA)-mediated hydrolysis (87). 2-AG is catabolized into AA and glycerol by different enzymes, such as monoacylglycerol lipase (MAGL), ABHD6, or ABHD12 (12, 75). Moreover, alternative endocannabinoid degradation pathways, such as the oxidation of AEA and 2-AG by cyclooxygenase, specific lipoxygenases, or even cytochrome *P*-450, have been identified (133).

Classical and nonclassical receptor binding of endocannabinoids. Endocannabinoids exert cannabimimetic actions via two G protein-coupled receptors (GPCRs), cannabinoid receptors 1 and 2 (CB_1 and CB_2) (30, 80, 90) (Fig. 2). These receptors are expressed in both central and peripheral organs. CB_1 receptors are mainly localized in the brain and central nervous system but are also present in peripheral organs, including peripheral nerves, such as enteric, sympathetic, and sensory nerves, and nonneuronal cells, such as liver, pancreas, and gastrointestinal epithelial cells (54, 61). CB_2 receptors are mainly located in peripheral organs, especially in spleen, and in immune cells (57, 95). However, CB_2 receptors have also been reported in brain, heart, gastrointestinal tract, vascular smooth muscle, and endothelial cells (89, 95, 103, 104).

AEA binds to central CB_1 receptors and, to a lesser extent, to peripheral CB_2 receptors (71, 100). 2-AG binds to CB_1 and CB_2 receptors with similar binding affinities and acts as a partial agonist of both receptors (127). Noladin ether binds to CB_1 receptors but only weakly to CB_2 receptors (42, 99). NADA preferentially binds to CB_1 receptors and is a more potent CB_1 agonist than AEA (11, 105). Virodhamine is a full agonist of CB_2 receptor and a partial agonist with in vivo antagonist activity at CB_1 receptor, although it is less potent than AEA at both receptors (102).

Endocannabinoids may have alternative targets other than classical CB_1 and CB_2 receptors. Transient receptor potential vanilloid type 1 (TRPV1) receptor is the best studied and is

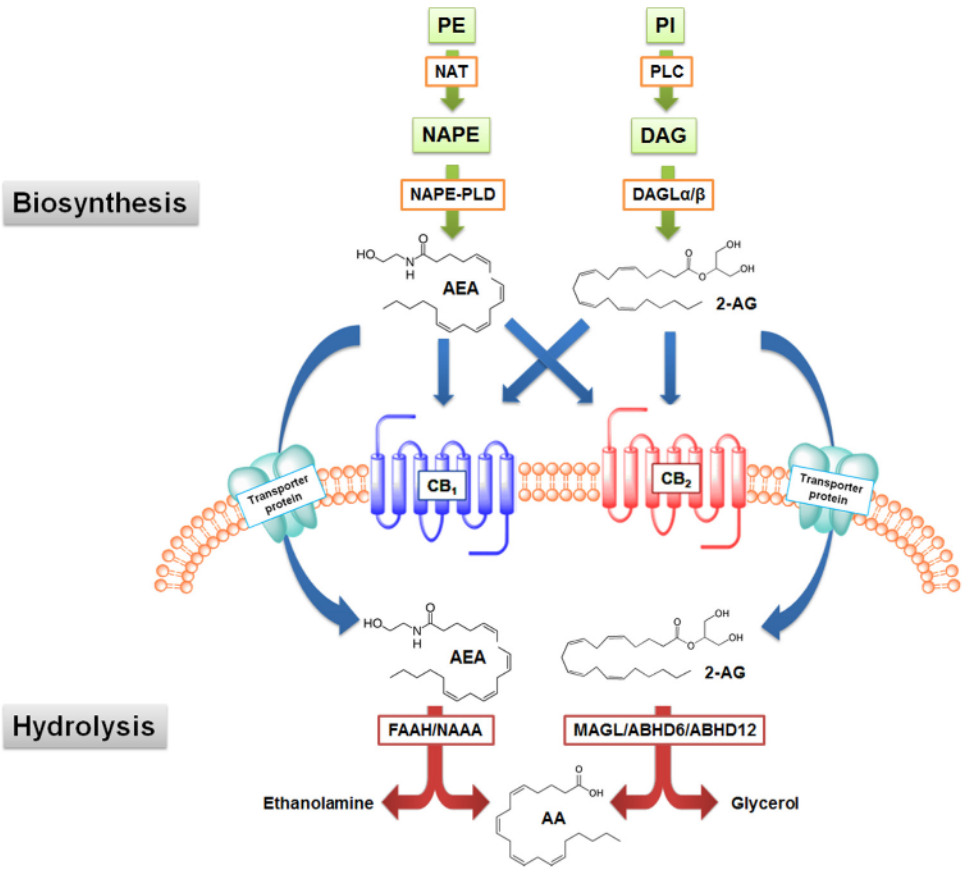


Fig. 1. Biosynthesis and hydrolysis of endocannabinoids. For the biosynthesis of *N*-arachidonoylethanolamine (AEA), phosphatidylethanolamine (PE) is converted to *N*-acylphosphatidylethanolamine (NAPE) by *N*-acyltransferase (NAT), and sequentially, NAPE-phospholipase D (NAPE-PLD) catalyzes NAPE and produces AEA. The biosynthesis of 2-arachidonoylglycerol (2-AG) begins with the phospholipase C (PLC)-mediated hydrolysis of the membrane lipid phosphatidylinositol (PI) to produce diacylglycerol (DAG), which is subsequently converted to 2-AG by diacylglycerol lipases (DAGL) α and β. After binding to cannabinoid receptors and exerting their biological activities, endocannabinoids are degraded by catalytic enzymes. AEA is degraded into arachidonic acid (AA) and ethanolamine by fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine-hydrolyzing acid amidase (NAAA)-mediated hydrolysis. 2-AG is catabolized into AA and glycerol by monoacylglycerol lipase (MAGL), α,β-hydrolase-6 (ABHD-6), and ABHD-12.

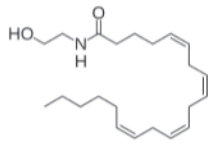
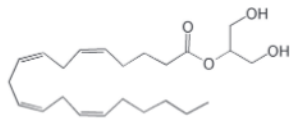
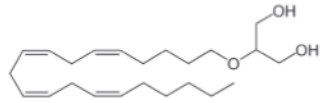
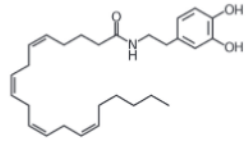
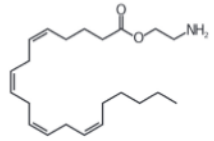
Name	Structure	CB_1/CB_2 receptor binding affinity	Alternative targets
AEA Anandamide		$CB_1>CB_2$ Partial agonist at both receptors	TRPV1 GPR55(?) PPARα PPARγ
2-AG		$CB_1=CB_2$ Partial agonist at both receptors	PPARβ/δ PPARγ
Noladin ether		$CB_1>CB_2$ CB_1-selective agonist	PPARα PPARγ
NADA		CB_1 Full agonist at CB_1	TRPV1
Virodhamine		$CB_1<CB_2$ Partial agonist at CB_1 Full agonist at CB_2	GPR55(?) PPARα

Fig. 2. Classical and nonclassical receptor binding of endocannabinoids. AEA, *N*-arachidonoylethanolamine; 2-AG, 2-arachidonoylglycerol; CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; GPR55, G protein-coupled receptor 55; NADA, *N*-arachidonoyl dopamine; noladin ether, 2-arachidonyl glyceryl ether; PPARα, peroxisome proliferator-activated receptor α; PPARβ/δ, peroxisome proliferator-activated receptor β or δ; PPARγ, peroxisome proliferator-activated receptor γ; TRPV1, transient receptor potential vanilloid type 1; virodhamine, *O*-arachidonoyl-ethanolamine.

mainly expressed by primary afferent neurons (32, 107). TRPV1 was originally identified as the receptor of capsaicin, the active ingredient of chili peppers (19). NADA was the first endogenous agonist of TRPV1 identified in mammals and activates TRPV1 as effectively as capsaicin (55). AEA acts as a full agonist for TRPV1, but it also indirectly affects TRPV1 activity by activating CB_1 receptor (112, 119). Other deorphanized GPCRs, such as GPR3, GPR6, GPR12, GPR18, GPR23, GPR40, GPR41, GPR43, GPR55, GPR84, GPR119, and GPR120, have also been suggested to be activated by cannabinoid receptor ligands (100), but, with the exception of GPR55, it has not been determined whether other GPCRs are directly targeted by cannabinoid receptor ligands. GPR55 is an orphan receptor that shows low sequence similarity with CB_1 and CB_2 receptors, but little sequence similarity with the ligand binding sites of either receptor (81, 100). The noncannabinoid lysophosphatidylinositol (LPI) has been reported to be an endogenous ligand of GPR55 (94). AEA and virodhamine were shown to be active at GPR55 by a [^{35}S]GTPγS binding assay, but result variabilities prevent classifying GPR55 as an endocannabinoid receptor (100, 111). AEA and virodhamine are also known to modulate GPR55 activity induced by LPI or other agonists (116). In addition, a number of cannabinoid receptor agonists have been shown to be peroxisome proliferator-activated receptor (PPAR) agonists in vitro (100). AEA, noladin ether, and virodhamine bind to PPARα, 2-AG binds to PPARβ/δ, and AEA, 2-AG, and noladin ether bind to PPARγ in a reporter gene assay and a competition assay using fluorescent ligands (14, 46, 47, 106, 128). Further studies are warranted to conclusively establish relationships between these alternative targets and endocannabinoids.

The Endocannabinoid System and Intestinal Diseases

Increasing evidence shows that the levels of endocannabinoids and/or CB receptors are altered in the biopsy samples of patients with intestinal diseases, such as diverticulitis, celiac disease, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and colon cancer, which suggests important roles of the endocannabinoid system in intestinal pathophysiology (4, 60, 63, 114) (Fig. 3).

Diverticulitis. Colonic diverticular disease (diverticulosis) is a common disorder with an undefined multifaceted pathogenesis. This disease is associated with aging and affects 65% or more of the population aged over 65 years in Western world due to reduced tensile strength of the colon wall (7, 136). In addition, dietary factors, such as low fiber intake, anatomic features of the colon, and even possible genetic effects play roles in the development of diverticulosis (7). Alterations of colonic motility have also been suggested to play a major etiological role and endocannabinoids are important modulators of neural contractile response in the colon (7, 50). Guagnini et al. (50) reported that tissue levels of AEA in diverticulitis (inflammation of diverticulum) were at least twice the

Disease		Diverticulitis	Celiac disease		IBS		IBD			CRC	
		Human	Human	Animal	Human		Human		Animal	Human	Animal
					IBS-D	IBS-C	CD	UC			
Ligands	AEA	Increased	Increased	Increased	No change	No change	Decreased	Increased or Decreased	Increased	Increased	No change
	2-AG	Decreased		Increased	Increased	No change	No change	No change	No change	Increased	Increased
Receptors	CB_1	No change (R,P)	Increased (R,P)		Genetic polymorphism	Genetic polymorphism	Increased (R,P) Genetic polymorphism	No change (R,P) or Increased (P) Genetic polymorphism	Increased (P)	Decreased (R,P)	No change (R)
	CB_2		Increased (R,P) Genetic polymorphism				Increased (P) or No change (R,P)	Increased (P) or No change (R,P)	Increased (R)	Increased (P) or No change (R)	No change (R)
	TRPV1				Increased (P)	Increased (P)					Decreased (R)
Metabolic enzymes (Synthesis)	NAPE-PLD		Increased (R,P)				Decreased activity	Decreased (P) Decreased Activity			
	DAGL							Increased (P)			
Metabolic enzymes (Hydrolysis)	FAAH		No change (R,P)		No change (R) Genetic polymorphism	Decreased (R)	Increased activity	No change (P) Increased activity			No change (R)
	MAGL							Increased (P)			
References		(50)	(8), (9), (25), (108)		(1), (15), (16), (44), (96)		(27), (35), (74), (122), (123), (139)		(2), (27), (77), (125)	(22), (68), (76), (135)	(58)

Fig. 3. Expression levels of the endocannabinoid system in intestinal diseases. AEA, *N*-arachidonoylethanolamine; 2-AG, 2-arachidonoylglycerol; CB_1, cannabinoid receptor 1; CB_2, cannabinoid receptor 2; CD, Crohn's disease; CRC, colorectal cancer; DAGL, diacylglycerol lipases; FAAH, fatty acid amide hydrolase; IBD, inflammatory bowel disease; IBS-C, IBS with colitis; IBS-D, IBS with diarrhea; MAGL, monoacylglycerol lipase; NAPE-PLD, *N*-acylphosphatidylethanolamine-phospholipase D; P, protein; R, mRNA; TRPV1, transient receptor potential vanilloid type 1; UC, ulcerative colitis.

control level, whereas 2-AG levels were slightly lower. The mRNA and protein expression levels of CB_1 receptor were similar in diverticular and control colons. Functional studies showed that the nonselective CB agonist WIN 55,212-2 was profoundly more potent at inhibiting contractions in controls than in diverticulitis strips and that the selective CB_1 antagonist SR141716 markedly increased twitch contraction in diverticular colons but had no effect in controls (50). These observations suggest that neural control of colonic motility is altered in diverticulitis and that the endocannabinoid system might contribute to these changes.

Celiac disease. Celiac disease is an inflammatory disease of the small bowel caused by a permanent intolerance to glutens in wheat and other cereal crops (66). Celiac disease is characterized by villous atrophy of small intestinal mucosa due to inflammatory injury and manifests symptoms of diarrhea, weight loss, weakness, and malabsorption (73). Celiac disease is associated with HLA class II molecules and almost all patients express HLA-DQ2 and/or HLA-DQ8, which suggests a strong genetic predisposition (121). These HLA-DQ molecules on antigen presenting cells bind to and then present modified gluten peptides to immunocompetent T cells in the small intestine, which initiates the disease (66, 73).

Accumulating evidence suggests that the endocannabinoid system contributes to celiac disease. In the jejunum of methotrexate (MTX)-treated rats, levels of AEA and 2-AG were increased in the active disease state and returned to basal levels at remission (25). This murine model is used to recapitulate celiac disease because MTX treatment has been shown to induce an enteropathy that resembles celiac mucosal lesions biochemically and histologically (26). Furthermore, AEA levels were reported to be elevated in the duodenal mucosa of the intestinal biopsy samples of patients with active celiac disease than in nonceliac individuals and to return to normal after remission on a gluten-free diet (25). Another study reported that the mRNA and protein levels of NAPE-PLD (the enzyme responsible for the synthesis of AEA) were higher in the duodenal mucosa of untreated celiac patients than in celiac patients on a gluten-free diet or normal controls, but that the expression levels of FAAH (the enzyme responsible for the degradation of AEA) were not significantly different in these three study groups (9). Interestingly, CB_1 receptor levels were markedly higher in the biopsy samples from patients with active celiac disease than in those of healthy controls or patients in remission. In particular, CB_1 receptors were detected in the subepithelial region of the duodenum, where gluten-reactive proinflammatory Th1 cells are located (25). Battista et al. (8) also reported that CB_1 and CB_2 mRNA and protein expression levels were upregulated in active disease and reverted to normal levels after treatment. In addition, small bowel biopsies from children with celiac disease revealed elevated levels of CB_2 receptor (108). In the same study, it was suggested that endocannabinoids were involved in non-HLA genetic susceptibility of celiac disease based on the finding that the CB_2 Q63R variant [a common missense variant (*rs*35761398) of *CNR2*, which encodes CB_2] increased the risk of celiac disease (108). Collectively, studies show that the levels of endocannabinoids and their receptors are increased in

active celiac disease but return to normal levels during remission, which strongly suggests that the endocannabinoid system plays a role in the development of celiac disease and that its targeting has therapeutic potential.

Irritable bowel syndrome. IBS is a common functional bowel disorder and about 10–20% of adults and adolescents suffer from its symptoms, which include abdominal pain or discomfort and impaired defecation (70). IBS subtypes can be classified based on predominant stool patterns as IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), and mixed IBS (IBS-M) (36, 70). The etiology of IBS has not been established but recent reports suggest the involvement of the endocannabinoid system in its pathophysiology. For example, the nonselective cannabinoid agonist dronabinol reduced fasting colonic motility in patients with IBS-D or IBS-M (137). In addition, FAAH mRNA levels in colonic biopsies of IBS-C patients were significantly lower than in healthy controls whereas there was no difference in the FAAH mRNA expression between IBS-D patients and healthy controls. Furthermore, 2-AG levels were higher but levels of OEA and PEA were lower in IBS-D patients than in healthy controls. On the other hand, OEA levels were higher in IBS-C patients than in healthy controls, and AEA levels were similar in IBS-C and IBS-D patients and controls (44). These findings suggest that slower turnover of endocannabinoids due to decreased FAAH levels in IBS-C patients may partially contribute to slowing of intestinal motility, a typical feature of IBS-C. Furthermore, cannabinoids have been reported to ameliorate visceral pain and hypersensitivity, and numbers of TRPV1-immunoreactive nerve fibers were found to be greater in colonic biopsies from IBS patients, which suggests that this increase contributes to visceral hypersensitivity and pain in IBS (1).

Interestingly, genetic polymorphisms of *CB_1* and *FAAH* genes have been associated with the symptoms of IBS. The CB_1 gene (*CNR1*) contains polymorphic triplet AAT repeats, and a higher number of AAT triplets may induce conformational changes in DNA and thereby alter gene transcription and reduce gene expression (53, 115). In one study conducted in a Korean cohort, the allele frequency of AAT triplet repeats in the *CNR1* gene was higher (10 or more) in IBS patients than in normal controls, and symptom scores for abdominal discomfort or pain were found to be higher in patients with more triplet repeats (96). Another genetic variant of *CNR1 rs*806378 (CC vs. CT/TT) shows a functional polymorphism, because the T allele of *CNR1 rs*806378 was found to be associated with altered nuclear protein binding in an electrophoretic mobility shift assay (131). Furthermore, *CNR1 rs*806378 (CC vs. CT/TT) showed a significant association with colonic transit in IBS-D, and in IBS patients with the *CNR1 rs*806378 CT/TT genotype the nonselective cannabinoid agonist dronabinol delayed colonic transit (16, 138). Genetic variation of the *FAAH* gene is also related with IBS. A single nucleotide polymorphism in the human *FAAH* gene (385C to A), which converts a proline residue to threonine (P129T), decreases FAAH protein expression (21). In the biopsy samples from functional gastrointestinal disorder patients, the odds of D-IBS and M-IBS were higher for the *FAAH* polymorphic (CA/AA) genotype than for the *FAAH* (CC) genotype (15). Furthermore, the CA/AA genotype was observed to be significantly associated with faster colonic transit than the *FAAH* CC genotype in IBS-D patients (15). The cannabinoid agonist dronabinol also reduced fasting proximal motility indexes in IBS-D patients with the *FAAH* CA/AA variant (137). These clinical studies indicate that polymorphic genotypes of *CB_1* and *FAAH* are highly associated with IBS and suggest their use as biomarkers to assess disease activity.

Emerging evidence indicates that endocannabinoids inhibit intestinal motility by activating CB_1 receptors. Activation of the endocannabinoid system reduced intestinal motility in mice, and this effect was enhanced in mice with croton oil-induced inflammation (62). For instance, the antitransit effect of cannabinoids was suppressed by the selective CB_1 receptor antagonist SR141716A, but not by the CB_2 receptor antagonist SR144528, suggesting the involvement of CB_1 receptor in the regulation of intestinal motility (62). In another study, pharmacological inhibitors of FAAH blocked intestinal motility and this effect was blunted in FAAH-deficient mice. Inhibition of FAAH increased AEA, 2-AG, and PEA levels and yet the effect of FAAH inhibitors was reduced by the CB_1 receptor antagonist rimonabant and by CB_1 deficiency, suggesting the involvement of CB_1 receptor in intestinal motility (18). In the same study, the authors found that decreased motility in FAAH-deficient mice did not achieve statistical significance as opposed to acute pharmacological inhibition. This suggests that congenital FAAH inactivation involves endogenous compensatory mechanisms that include a failure to increase the levels of 2-AG and PEA (both of which are inhibitors of gastrointestinal motility) (18).

Cannabinoids also have a potent antipropulsive effect. Generally, this effect is related to inhibition of the release of acetylcholine from excitatory motor neurons, which partially mediate the ascending contraction phase of the peristaltic reflex, by CB_1 receptors (98). AEA decreased ascending contractions and concomitant substance P release and reduced descending relaxation and concomitant vasoactive intestinal peptide release via CB_1 receptors (49). Furthermore, the CB_1 receptor antagonist AM251 but neither the CB_2 receptor antagonist AM630 nor the TRPV1 receptor antagonist resiniferatoxin increased those responses (49). Moreover, AEA or 2-AG suppressed colonic cholinergic contractility in strips of human colonic longitudinal muscle and circular muscle in vitro (120). In addition, electrically evoked contractile responses in human ileum longitudinal smooth muscle were decreased by the CB_1 receptor antagonist SR141716, but not by the CB_2 receptor antagonist SR144528 (24). In contrast, CB_2 receptors had no significant effects on gut motility under normal conditions but were found to regulate motility under pathological conditions (126). In one study, the CB_1 receptor agonist ACEA inhibited basal gastrointestinal transit in rats, while the CB_2 agonist JWH-133 decreased lipopolysaccharide (LPS)-mediated increases in gastrointestinal transit (79). In addition, activation of CB_2 receptors by JWH-133 in the enteric nervous system decreased LPS-enhanced intestinal contractility (37). Thus it appears cannabinoids are potent inhibitors of propulsive motility and this effect is probably mediated by the action of CB_1 receptors.

CB_1 antagonists have been suggested as treatments for constipation. The CB_1 receptor inverse agonist taranabant reversed experimental constipation, suggesting that CB_1 receptor be considered a potential target in IBS-C (43). In biopsy samples of patients with slow-transit constipation, the expression level and activity of enteric FAAH were decreased but

AEA and 2-AG levels were increased vs. normal controls (140). In a recent study it was reported that the DAGL inhibitors reversed pharmacologically slowed gastrointestinal motility and intestinal contractility and normalized fecal output in constipated C3H/HeJ mice via 2-AG and CB_1 receptor-dependent mechanisms (6). These findings indicate that the inhibition of endocannabinoid biosynthesis offers potential novel way of treating constipation.

Inflammatory bowel disease. IBD including Crohn's disease (CD) and ulcerative colitis (UC) is chronically relapsing-remitting or progressive inflammatory conditions of the gastrointestinal tract with complex etiologies that involve genetic, environmental, microbial, immune, and nonimmune factors (29). A recent systemic review reported that the worldwide incidence and prevalence of IBD are increasing (86). The main symptoms of IBD include abdominal pain, diarrhea, rectal bleeding, and weight loss (134). Anti-inflammatory drugs, such as sulfasalazine, mesalazine, and glucocorticosteroids, and more recently immunomodulators have been widely used for IBD treatment.

Cannabinoids have been used to treat inflammatory conditions in the gut. In a retrospective observation study, 30 CD patients stated that the use of cannabis ameliorated disease activity and reduced the need for other conventional medicines, such as steroids (92). According to another cohort study of 100 UC and 191 CD patients, 33% of UC and 50% of CD patients were lifetime users of cannabis to relieve IBD-related symptoms including abdominal pain and diarrhea (67). In a prospective placebo-controlled study of 21 CD patients, a short course (8 wk) of cannabis provided significant clinical benefits, such as a steroid-free status and improved appetite and sleep in 90% of patients with active CD (91). These experiences and observations suggest that cannabis be a potential candidate for the development of an anti-IBD therapy and that the endocannabinoid system can be used beneficially in IBD (93).

The levels of endocannabinoids and/or their receptors are altered in IBD. Clinically, AEA levels were highly elevated (>2-fold) in mucosal biopsies of active UC patients vs. normal control biopsies (27). In another study, AEA levels were significantly lower in inflamed than in uninflamed IBD mucosa. In parallel, the activity of the AEA-synthesizing enzyme NAPE-PLD was lower and that of the AEA-degrading enzyme FAAH was higher in inflamed than in uninflamed mucosa (35). In the same study, the expression of CB_1 receptor was significantly elevated in the inflamed mucosa of CD and UC patients, while the expression of CB_2 receptor was similar in inflamed and uninflamed tissues. Quantification of mucosal immunoreactivity revealed that CB_2 receptor expression (but not CB_1 receptor expression) and the expressions of DAGLα and MAGL were elevated in mild and moderate UC patients but that NAPE-PLD expression was decreased in moderate and severe UC patients, suggesting dysregulation of AEA and 2-AG (74). An immunohistochemical study indicated that CB_1 and CB_2 receptors are present in human colonic epithelium, smooth muscle, and submucosal myenteric plexus (139). In lamina propria, CB_1 and CB_2 receptors are expressed in plasma cells, whereas only CB_2 receptors are expressed in macrophages. One study showed that CB_2 receptors are especially increased in the colonic tissues of IBD patients, while another showed that CB_1 mRNA expression (but not CB_2 mRNA expression) was upregulated in the colonic tissues of CD patients (122, 139). Intriguingly, a genetic polymorphism of the CB_1 receptor gene *CNR1* 1359 G/A was reported to influence susceptibility to UC and CD phenotype (123). However, data derived from human subjects are not enough to draw a conclusion about the role of the endocannabinoid system in IBD. When CB_1 receptor is elevated, CB_2 receptor is elevated or unchanged, and vice versa.

Studies using experimental animal models of IBD have also shown that the endocannabinoid system plays an essential role in colitis. In the colons of 2,4-dinitrobenzene sulfonic acid (DNBS)-treated mice and in colonic submucosa of trinitrobenzene-sulfonic acid (TNBS)-treated rats, AEA levels (but not 2-AG levels) were strongly elevated vs. untreated controls (27). Another study also showed that AEA levels were elevated in the colons of TNBS and dextran sodium sulfate (DSS)-treated mice vs. controls (2). In addition, MAGL inhibitor-induced increases in endogenous 2-AG levels significantly decreased colonic damage and proinflammatory cytokine production in TNBS-induced colitis (3). Moreover, the administration of the NAAA chemical inhibitor AM9053 reduced TNBS-induced colitis by reducing leukocyte infiltration and activation and decreasing the expressions of proinflammatory cytokines, which may have been caused by increased AEA levels, because the hydrolysis of AEA is blocked by AM9053 (2). As a result, the levels of endocannabinoids were often increased in inflamed intestine, and boosting endocannabinoid levels by administering biochemical inhibitors reduced this inflammation.

The tissue levels of cannabinoid receptors are also altered in the presence of intestinal inflammation. CB_1 expression was increased in myenteric neurons of colons from DNBS-treated mice, and genetic and pharmacological blockade of CB_1 increased the severity of DNBS- and DSS-induced colitis, and consistent treatment with a CB_1 agonist and genetic ablation of FAAH protected against DNBS-induced colitis (77). Inhibitor of endocannabinoid membrane transporter, FAAH inhibitor, or a combination of both inhibitors ameliorated TNBS-induced colitis in mice, and these effects were diminished in CB_1 or CB_2 receptor knockout mice (124). However, another study reported that FAAH inhibition with two potent and selective inhibitors (PF-3845 and URB597) did not improve colon inflammation in a TNBS-induced colitis model (2). In mustard oil- and DSS-induced colitis, CB_1 and CB_2 agonists both inhibited colitis by improving colon length, ameliorating disease symptoms, and reducing histological inflammatory scores (65). In TNBS-induced colitis, CB_2 mRNA expression was significantly increased in colons, and activation of CB_2 receptor by selective agonists (JWH-133 and AM1241) reduced colitis, whereas treatment with the CB_2 receptor antagonist AM630 exacerbated colitis (125). In another study, CB_1 receptors limited and reduced DNBS-induced inflammation in the enteric nervous system and in the smooth muscle, indicating that a genetic deficiency of CB_1 would abolish this protective effect and cause membrane potential instability and prolonged inhibitory junction potentials in circular smooth muscle (117). A study using mice lacking CB_1 and/or CB_2 receptor showed that genetic deletion of either receptors aggravated TNBS colitis, but the absence of both receptors did not exacerbate colitis severity compared with the absence of each receptor (38). In mice, the centrally active CB_1/CB_2 receptor agonist WIN 55,212-2 blocked DSS- and TNBS-induced colitis,

whereas SAB378, a peripherally restricted CB_1/CB_2 receptor agonist, had no effect on colitis, suggesting that peripheral CB receptor stimulation alone is not sufficient to exert an anti-inflammatory effect (23). However, there remains a possibility that the doses of SAB378 used in this study were not sufficient to induce an anti-inflammatory effect, as the doses used were lower than those of other cannabinoid agonists used in colitis models or the doses of WIN 55,212-2 used in the same study, as mentioned by Alhouayek and Muccioli (4). Spontaneous colitis in IL-$10^{-/-}$ mice was reduced by the CB_2 receptor agonist JWH-133 and this was attributed to the inactivation of inflammatory cells (118). Overall, data from animal studies suggest that the expression levels and/or activities of cannabinoid receptors are closely related to intestinal inflammation. However, available information does not fully explain the role of endocannabinoids in IBD.

Activation of CB_1 or CB_2 receptors by their agonists (WIN 55,212-2 and JWH-015, respectively) reduced colitis-induced hypersensitivity to colorectal distension in rats, whereas only the CB_1 receptor antagonist rimonabant increased inflammatory hyperalgesia, suggesting that only CB_1 receptor is involved in colitis-induced abdominal response to colorectal distension (colitis-induced hyperalgesia) (113).

A selective TRPV1 receptor antagonist decreased microscopic colitis induced by TNBS and subsequent visceral hyperalgesia, thus indicating that TRPV1 receptor plays an important role in the generation of inflammation and hypersensitivity (85). Furthermore, numbers of TRPV1 expressing sensory nerve fibers were reported to be increased in patients with rectal hypersensitivity and fecal urgency, which could be a feature of IBD (20). In addition, TRPV1-deficient mice showed increased susceptibility to DNBS-induced colitis; this endogenous protective effect of TRPV1 receptors was attributed to the modulation of colonic electrophysiological properties (78, 117).

Colorectal cancer. Colorectal cancer (CRC) is the third most common malignancy and the fourth most common cause of cancer-related death, and in Asia and Africa its incidence is gradually increasing presumably due to the adoption of Western lifestyles (129). About 20–30% of all CRC cases have a familial basis, but the majority have been associated with environmental factors (110, 130). Chronic intestinal inflammation, such as that observed in IBD, also increases the risk of CRC, and such cases are referred to as colitis-associated colorectal cancer (130). Recent studies have elucidated important interactions between the endocannabinoid system and cancer, and abnormal regulation of the endocannabinoid system is known to contribute to cancer progression in several different types of cancer (52). As a result, pharmacological targeting of the endocannabinoid system is emerging as a promising new cancer therapy (10).

Abnormal expression patterns of cannabinoid receptors in CRC have been reported by several studies. In particular, the mRNA and protein levels of CB_1 receptors were found to be greatly reduced in human CRC tissues compared with adjacent normal mucosae and in 9 of 10 human cancer cell lines, and this effect was attributed to aberrant methylation of CpG islands within CB_1 promoter (135). In contrast, the mRNA expression levels of CB_2 receptors were not different in CRC and normal tissues (135). In another study, CB_1 receptor levels were found to be downregulated in tumor tissues vs. paired normal mucosae, whereas CB_2 receptor levels were upregulated in tumor specimens vs. paired normal mucosa (22). According to a recent study, which was conducted on tissue samples of 175 CRC patients, CB_2 receptor expression was increased in tumor tissues of CRC patients compared with their normal counterparts, and tumors with higher CB_2 receptor levels also exhibited higher proliferation levels, suggesting CB_2 receptor expression might be a marker of poor prognosis (76). In animal studies, genetic or pharmacological (AM251) deletion of CB_1 receptor enhanced intestinal tumor growth in $Apc^{min/+}$ mice, in which multiple intestinal polyps develop spontaneously as in humans due to a germ-line mutation in the *APC* gene, but activation of CB_1 receptor by its agonist (R-1 methanandamide) attenuated tumor growth (135). In a mouse xenograft model, the CB_2 receptor agonist CB13 reduced human colon cancer cell growth (22). In an azoxymethane (AOM)-induced tumor model, CB_1 and CB_2 receptor mRNA expressions were unchanged but TRPV1 receptor mRNA expression was significantly decreased in AOM-treated mouse colons vs. control colons (58). Moreover, FAAH inhibitor and the cannabinoid receptor agonist HU210 significantly reduced AOM-mediated aberrant crypt foci (ACF) formation, and ACF numbers were not different in CB_1 receptor-deficient and wild-type mice (58). Although altered expression levels of cannabinoid receptors have been observed in several studies, the relationship between cannabinoid receptors and CRC is obviously more complex than straightforward cause-and-effect.

The levels of endocannabinoids were also altered in CRC. In AOM-treated mouse colons, the levels of 2-AG were significantly increased but the levels of AEA were unaltered. In addition, FAAH inhibitor increased 2-AG and AEA levels significantly (58). In another study, AEA and 2-AG levels were three- and twofold higher in human tissues of transformed adenomatous polyps and CRC, respectively, compared with normal mucosae (68). Collectively, these results suggest that endocannabinoids might act as endogenous inhibitors of cancer growth.

The endocannabinoid system modulates tumor progression by regulating apoptosis. Treatment of mouse with AOM suppressed the activations of caspase-3 and caspase-9 and thus inhibited apoptosis and promoted tumor growth, and cotreatment of the FAAH inhibitor *N*-arachidonoylserotonin reversed this effect of AOM on caspase-3 inactivation and reduced aberrant crypt foci formation (58). In colon cancer cells, the activations of CB_1 and CB_2 receptors caused apoptosis via TNF-α-mediated de novo synthesis of ceramide; in this background, the CB_1 receptor agonist R-1 methanandamide promoted apoptosis by downregulating the antiapoptotic protein survivin via the cyclic AMP-dependent protein kinase A signaling pathway (22, 135). Interestingly, AEA inhibited the growth of COX-2-expressing CRC cells by inducing cell death, and this effect was enhanced by inhibiting FAAH but partially prevented by inhibiting COX-2 activity, indicating that AEA might be therapeutically useful against CRC, which overexpresses COX-2 and develops resistance to apoptosis (97). The proliferation and migration of cancer cells can be modulated by the endocannabinoid system. AEA, 2-AG, and the CB receptor agonist HU-210 inhibited the proliferation of human colon cancer Caco-2 cells expressing only CB_1 receptor, and these inhibitions were blocked by the CB_1 receptor antagonist

SR141716A but not by the CB_2 receptor antagonist SR144528 (68). Moreover, the activations of both CB receptors inhibited the proliferation of DLD-1 cells expressing CB_1 and CB_2 receptors (68). In another study, the upregulation of CB_2 receptor in CRC tissues was found to be related to higher proliferation levels in tumors (76). Furthermore, the activation of CB_2 receptor caused *SNAIL1* overexpression and a direct correlation was observed between CB_2 receptor and *SNAIL1* expression in human tumors, indicating a positive correlation between CB_2 receptor expression and *SNAIL1* expression, the latter of which is related to the epithelial mesenchymal transition process, the first step in cancer metastasis (76). It was also reported that CB_1 receptor activation by AEA inhibited the norepinephrine-induced migration of human colon cancer SW480 cells (64). Thus it seems that endocannabinoids and their receptors modulate tumor progression by regulating cell death and/or proliferation.

Cannabidiol has been shown to have analgesic, anti-inflammatory, antioxidant, and neuroprotective effects (59). This nonpsychotropic cannabinoid has very low binding affinity for CB_1 and CB_2 receptors and may inhibit FAAH (28, 59). Cannabidiol has also been suggested to have potential therapeutic effects in the context of colon carcinogenesis (58). Similar to the effect of endocannabinoids on CRC, cannabidiol reduced numbers of AOM-induced ACF, polyps, and tumors in a mouse colon cancer model and suppressed AOM-induced Akt phosphorylation and caspase-3 inactivation in colonic tissues. In Caco-2 cells, cannabidiol reduced H_2O_2-mediated DNA damage, increased 2-AG levels, and exerted an antiproliferative effect in a CB_1- and TRPV1-dependent manner (5). In human CRC cells, the major active component of marijuana Δ^9-THC induced apoptosis dose dependently by activating caspase-3 and increasing cleavage of its substrate, poly ADP-ribose polymerase (PARP) (48). Notably, THC-induced apoptosis was blocked by the CB_1 receptor antagonist AM251, but not by the CB_2 receptor antagonist AM630 (48). In addition, activation of CB_1 receptor by THC effectively inhibited two major cell survival signaling pathways, the RAS-MAPK/ERK and PI3K/AKT pathways, and this inhibition was accompanied by activation of the proapoptotic Bcl-2 family member BAD (48). In Caco-2 cells, cannabigerol decreased cancer cell viability and increased ROS production in time- and concentration-dependent manner, and these effects were not affected by the activations of TRP channels (TRPA1, TRPV1, or TRPV2) but were enhanced by the CB_2 receptor antagonist AM630 (13). Furthermore, cannabigerol inhibited the growth of xenograft tumors (HCT116) and AOM-induced carcinogenesis (13). By and large, studies about therapeutic effects of cannabinoids may provide an insight into the possible application of endocannabinoids to anticancer therapy.

The Endocannabinoid System and the Gut Microbiota

Gut microorganisms play critical roles in energy balance by contributing to host metabolism. Emerging evidence suggests that the gut microbiota modulate the endocannabinoid system to regulate energy metabolism and gastrointestinal function (17). The first study to link the endocannabinoid system and gut bacteria was performed by Rousseaux et al. (109), who showed that CB_2 receptor expression was increased by treating intestinal epithelial cells with a *Lactobacillus acidophilus* strain, and that oral administration of this strain reduced abdominal pain in rats. Several studies have also shown that LPS (a component of the cell walls of gram-negative bacteria) influences the levels of endocannabinoids. For example, LPS induced AEA synthesis in macrophages, downregulated FAAH expression, and increased AEA production in peripheral lymphocytes (69, 72). Gut bacteria also modulate the expression of the intestinal endocannabinoid system, which in turn regulates adipogenesis (88). Administration of *Akkermansia muciniphila* (a mucin-degrading bacterium that resides in the intestinal mucus layer) to high-fat diet-fed mice increased the levels of 2-AG, 2-OG, and 2-PG in intestine and reversed high-fat diet-induced metabolic disorders (39). Furthermore, modulation of the innate immune system has been linked to the gut microbiota and the endocannabinoid system. For example, deletion of *MyD88* (an adaptor molecule of Toll-like receptors) in the intestinal epithelium altered the composition of gut microorganisms and increased the levels of 2-AG and 2-OG but decreased AEA levels (40). Although the gut microbiota and the endocannabinoid system have been shown to be linked in various human diseases, the molecular basis of this link has not been established, and no direct link has been conclusively demonstrated in humans.

Conclusion

Convincing evidence suggests that the endocannabinoid system is expressed in the gut and maintains intestinal homeostasis by modulating many important functions including the immune system, motility, sensation, and secretion. Dysregulation of the endocannabinoid system may contribute to the developments of several intestinal disorders, such as diverticulitis, celiac disease, IBS, IBD, and CRC. Accordingly, many components of the endocannabinoid system have been suggested to be pharmacological targets. However, the expression levels of the endocannabinoid system in a variety of diseases are somewhat variable and often ambiguous, and the extended list of endocannabinoid-related mediators makes things more complex. Therefore, further studies are required to define how the endocannabinoid system regulates intestinal functions in health and disease and to provide options for the therapeutic exploitation of the endocannabinoid system to counteract disease progression in the gut.

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AUTHOR CONTRIBUTIONS

Y.L. and E.I. prepared figures; Y.L., J.J., and E.I. drafted manuscript; Y.L., J.J., H.Y.C., C.P., and E.I. edited and revised manuscript; Y.L., J.J., H.Y.C., C.P., and E.I. approved final version of manuscript; E.I. conceived and designed research.

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