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Review

Role of Gut Microbiota-Gut Hormone Axis in the Pathophysiology of Functional Gastrointestinal Disorders

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Gut microbiota exert a pivotal influence on various functions including gastrointestinal (GI) motility, metabolism, nutrition, immunity, and the neuroendocrine system in the host. These effects are mediated by not only short-chain fatty acids produced by microbiota but also gut hormones and inflammatory signaling by enteroendocrine and immune cells under the influence of the microbiota. GI motility is orchestrated by the enteric nervous system and hormonal networks, and disturbance of GI motility plays an important role in the pathophysiology of functional gastrointestinal disorders (FGIDs). In this context, microbiota-associated mediators are considered to act on specific receptors, thus affecting the enteric nervous system and, subsequently, GI motility. Thus, the pathophysiology of FGIDs is based on alterations of the gut microbiota/gut hormone axis, which have crucial effects on GI motility.
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Key Words
Enteric nervous system; Functional gastrointestinal disorders; Gastrointestinal hormones; Irritable bowel syndrome; Microbiome

Introduction

Although the pathogenesis of functional gastrointestinal disorders (FGIDs) is multifactorial, gastrointestinal (GI) dysmotility, and visceral hypersensitivity play a central role.[1] Recently, much attention has been focused on gut microbiota, as it has become clear that alterations in the gut microenvironment are significantly involved in the pathophysiology of various diseases such as GI disease, metabolic syndrome, autoimmune disease, and nervous/endocrine system disorders.[2] Gut microbiota have a complex influence on metabolism, nutrition and immune function in the host, and therefore disruption or alteration of the microbiota plays a pivotal role in GI inflammatory and/or FGIDs. Gut hormones also have central mediating roles in GI motility, appetite and body energy metabolism via the brain-gut axis, and thus also have pivotal involvement in FGIDs whose characteristic symptoms are closely associated with food intake. The present review provides a broad outline of interactions between the gut microbiota and gut hormone axis in relation to GI motility in the pathophysiology of FGIDs.

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Role of Gut Hormones in the Pathophysiology of Functional Gastrointestinal Disorders

The motility of the GI tract is mediated by both neural and hormonal networks. Gut hormones are released from enteroendocrine cells scattered along the GI tract (comprising fewer than 1% of all GI epithelial cells),[3] which play prominent roles in the hormonal networks during the interdigestive and postprandial periods. At present, more than 30 gut hormones have been isolated. Interestingly, the gut hormones that function in GI motility also affect appetite and body energy metabolism, suggesting that feeding behavior and GI motility are cooperatively regulated by gut hormone secretion (Table 1).

Gut Hormones Affecting Interdigestive Motility

Motilin

Motilin, which is produced mainly by M cells in the duodenum during the interdigestive period, promotes phase III activity of the migrating motor complex and gastric contraction. Erythromycin, a motilin receptor agonist, increases gastric emptying and not only alleviates gastroparesis but also mediates blood glucose control in diabetic patients.[4] However, clinical use of erythromycin for dysmotility is thought to be difficult, as its continuous use causes dysbiosis of the gut flora.

Ghrelin

In 1999, ghrelin was isolated from the stomach as the endogenous ligand of growth hormone secretagogue receptor 1a.[5] Ghrelin is produced and secreted by X/A-like cells in the stomach (especially the fundus)[5] and stimulates appetite and food intake.[6] In addition, accumulating evidence has clarified that ghrelin stimulates both gastric motility and gastric acid secretion.[7,8] Ghrelin stimulates GI motility by acting on not only neuropeptide Y, the preganglionic dorsal vagal complex and vagal afferent neurons, but also intrinsic cholinergic neurons in the GI tract,[9-12] and these effects are remarkably abolished by bilateral vagotomy.[7]

Table 1. Profile of Gut Hormones

Gut hormones	Site of secretion	Endocrine cells	Localization of receptors	Roles in gastrointestinal motility
Motilin	Duodenum, jejunum	M-cells	Vagal nerve	Promotes phase III MMC activity
			CNS	Accelerates gastric contraction
Ghrelin	Stomach, duodenum, jejunum	X/A-cells	Vagal nerve	Suppresses motilin release
			CNS	Suppresses phase III MMC activity
CCK	Duodenum, jejunum	I-cells	Gastrointestine	Triggers gallbladder emptying
			Gallbladder	Slows gastric emptying
			Vagal nerve	Accelerates small intestinal transit
			Enteric neurons	
			CNS	
GIP	Duodenum, jejunum	K-cells	Enteric neurons	Reduces phase III MMC activity
			CNS	Slows small intestinal transit
GLP-1	Ileum, colon	L-cells	Enteric neurons	Slows gastric emptying
			Immune cells	Slows small intestinal transit
			CNS	Inhibits colonic transit
PYY	Ileum, colon	L-cells	Enteric neurons	Slows gastric emptying
			CNS	Slows small intestinal transit
				Inhibits colonic transit
Serotonin (5-HT)	Whole GI tract	EC cell	Enteric neurons	Accelerates gastric emptying
			Muscle cells	Accelerates gastric accommodation
			Immune cells	Initiates peristaltic reflex and propulsive motility
			Vagal nerve	Induces slow excitatory postsynaptic potentials
			CNS	Triggers colonic migrating motor complexes

CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; PYY, peptide YY; 5-HT, 5-hydroxytryptamine; GI, gastrointestinal; EC, enterochromaffin; CNS, central nervous system; MMC, migrating motor complex.

Gut Hormones Affecting Postprandial Motility

Cholecystokinin

Cholecystokinin (CCK) was discovered in jejunal extracts as a gallbladder contraction factor.[13] CCK is abundantly synthesized in small-intestinal I-cells and cerebral neurons. In addition, CCK is expressed in various endocrine glands (pituitary, thyroid, pancreatic islets, adrenal, and testis), peripheral nerves and kidney.[14] Indeed, CCK plays roles in not only digestive function (pancreatic enzyme secretion and gut motility) but also neurotransmission in the cerebral and peripheral neuron systems.[14] In the context of gut motility, it has been reported that exogenous CCK suppresses antral and duodenal motility,[15] whereas CCK receptor antagonist accelerates gastric emptying.[16] CCK is able to excite mucosal vagal afferent fibers in the stomach and regulate postprandial gastric emptying and satiation largely via the vagal pathway.[17-19] On the other hand, small-intestinal transit time is shortened by stimulation with exogenous CCK, and prolonged by CCK receptor antagonist.[20] In the colon, CCK administration does not affect human rectal motor function.[21]

Glucose-dependent insulinotropic polypeptide

Glucose-dependent insulinotropic polypeptide (GIP; also known as gastric inhibitory polypeptide) is produced mainly by K cells in the duodenum[22] and stimulates insulin secretion as an incretin hormone in a glucose-dependent manner. In addition, GIP is likely to inhibit gastric acid secretion and gastric emptying in animals, whereas these inhibitory effects remain unclear in humans.[22] On the other hand, triglyceride disposal and adipose uptake of fatty acids may be important functions of GIP in humans.[23]

Glucagon-like peptide 1

Glucagon-like peptide 1 (GLP-1) is secreted predominantly from L cells in the ileum and colon and released as an incretin hormone in response to enteral nutrient exposure.[24] GLP-1 as well as GIP stimulates insulin secretion and is rapidly degraded by dipeptidylpeptidase-4 (DPP4).[25] In this context, not only GLP-1 agonist but also the DPP4 inhibitor was developed as a therapeutic medicine for diabetes. Of note, GLP-1 also plays a role in postprandial GI motility. Studies using endogenous/exogenous GLP-1 and/or DPP4 inhibitors have revealed that GLP-1 slows gastric emptying and intestinal motility.[26] Moreover, recent evidence has suggested that GLP-1 inhibits postprandial GI motility through the GLP-1 receptor at myenteric neurons, involving nitrergic and cAMP-dependent mechanisms.[27,28]

Peptide YY

Peptide YY (PYY) is secreted mainly from L cells in the ileum and colon[29] and degraded by DPP4,[30] similarly to GLP-1. Furthermore, the function of PYY resembles that of GLP-1; thus, PYY is likely to suppress appetite, slow gastric emptying and inhibit small-intestinal motility.[31] Endogenous PYY acts via neuronal Y2 receptors to inhibit colonic transit.[32]

Serotonin

Serotonin, also termed 5-hydroxytryptamine (5-HT), functions as both a neurotransmitter in the CNS and a local hormone in the GI tract. More than 90% of the body's 5-HT is synthesized in the gut (approximately 90% of 5-HT originates from enterochromaffin (EC) cells and 10% from enteric neuron cells).[33] Tryptophan hydroxylase-1 is the rate-limiting enzyme for biosynthesis of 5-HT, and serotonin reuptake transporter (SERT) terminates the actions of 5-HT by removing it from the interstitial space.[34] 5-HT has motor function through interaction with neurons within the myenteric and submucosal plexuses, intrinsic and extrinsic sensory neurons, and EC cells. Among the 7 subtypes of serotonin receptors, 5-HT_3 and 5-HT_4 receptors have been most studied in the context of GI motility.[35] 5-HT released by mucosal mechanical and chemical stimuli is capable of inducing the mucosal peristaltic reflex, and hence propulsive peristalsis, and also affects the colonic migrating motor complexes.[35]

Dysregulation of Gut Hormone in Functional Gastrointestinal Disorders

FGIDs are defined by symptom-based diagnostic criteria that combine chronic or recurrent symptoms attributable to the GI tract in the absence of other pathologically based disorders. A number of factors are involved in the pathophysiology of FGIDs, including visceral sensitivity, GI motility, GI mucosal immunity, gut microbiota, and psychosocial stress in brain-gut interaction.[1] Gut hormones have been proposed as key mediators of these factors in the brain-gut axis and are indeed involved in the development and/or exacerbation of FGID symptoms (Tables 2 and 3), as described below.

Functional dyspepsia

Functional dyspepsia (FD) is a heterogeneous disorder associated with abnormalities of gut motor function, including initially accelerated or delayed gastric emptying, impaired proximal gastric relaxation, increased perception of gastric distension, and disordered antro-duodenal motility.[36]

Table 2. Dysregulation of Gut Hormones in Functional Dyspepsia

Gut hormone	Published year	Clinical evidences for gut hormone in FD	Reference No.
Motilin	2000	ABT-229 (motilin agonist) does not relieve the symptoms in FD patients.	38
	2005	Exogenous motilin stimulation inhibits proximal gastric accommodation in FD patients.	36
	2008	Camicinal accelerates gastric emptying (35-60%) in patients with gastroparesis.	40
	2016	Motilin receptor agonist (camicinal; GSK962040) accelerates gastric emptying and increases glucose absorption in feed-intolerant critically ill patients.	39
Ghrelin	2004	The plasm ghrelin concentration may be decreased in accordance with the progression of gastric atrophy due to *H. pylori* infection.	45
	2005	Plasma acylated ghrelin levels are correlated with symptom score in FD patients.	43
	2006	Ghrelin, a novel appetite-promoting gastrointestinal peptide that also promotes gastric motility or basal acid secretion may be a therapeutic target for FD treatment.	44
	2007	Fasting desacyl and total ghrelin levels are significantly lower in FD patients than in controls, but active ghrelin levels are similar between 2 groups in both fasting and postprandial periods.	41
	2008	Ghrelin treatment tends to increase daily food intake in FD patients.	46
	2009	Acylated ghrelin levels are significantly lower in NERD and PDS patients than in healthy volunteers.	173
		Abnormally low preprandial ghrelin levels and absence of significant postprandial decrease of ghrelin levels are present in a subset of dysmotility-like FD patients.	42
	2013	The preproghrelin 3056TT genotype is significantly associated with the acylated ghrelin levels and the feeling of hunger in *H. pylori*-negative FD patients.	174
	2015	The serum ghrelin level 30 minutes after breakfast is significantly higher in dyspepsia patients than in controls.	175
		FD-PDS is associated with lower fasting and maximum acyl ghrelin concentrations and dampened acyl ghrelin flux.	176
CCK	1994	FD patients with CCK-8 stimulation show stronger symptoms of dyspepsia compared with healthy control.	48
	2008	Fasting and postprandial plasma CCK is greater in FD patients.	47
	2014	Following lipid infusion, the mean mucosal CCK concentration is lower in FD patients compared with healthy volunteers.	177
GIP and GLP-1	2014	Increased sensitivity to enteral dextrose and lipid infusions is associated with greater plasma GIP and GLP-1 concentrations in FD.	51
	2016	GLP-1 concentration is similar in FD patients and controls, but postprandial GLP-1 secretion may correlate with nausea in FD patients.	52
PYY	2008	Fasting and postprandial PYY are lower in FD patients than in healthy subjects.	47
	2014	PYY concentrations in response to dextrose and lipid infusions are higher in FD patients with impaired glucose tolerance.	51
Serotonin (5-HT)	2011	Serotonin receptor 3A polymorphism HTR3A c.-42T is associated with severe dyspepsia.	54
		Serotonin transporter gene polymorphism may be associated with functional dyspepsia in a Japanese population.	55
	2013	Patients with FD have lower basal and postprandial plasma levels of serotonin.	56

FD, functional dyspepsia; *H. pylori*, *Helicobacter pylori*; NERD, non-erosive reflux disease; PDS, postprandial distress syndrome; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; PYY, peptide YY; 5-HT, 5-hydroxytryptamine.

Table 3. Dysregulation of Gut Hormones in Irritable Bowel Syndrome

Gut hormone	Published year	Clinical evidences for gut hormone in IBS	Reference No.
Motilin	1985	Circulating motilin is positively correlated with symptoms in functional bowel disorders.	59
	1996	The IBS patients have reduced motilin secretion after both water intake and the fat meal.	60
	2005	Higher motilin levels are observed in IBS in both interdigestive and postprandial periods.	61
Ghrelin	2009	The number of ghrelin-positive cells is increased in IBS-D patients.	66
		The low densities of ghrelin cell is found in IBS-C patients.	66
CCK	2006	IBS patients have increased fasting and postprandial plasma levels of CCK	178
	2010	Post-infectious IBS patients have increased numbers of CCK cells in the duodenum.	70
	2015	The densities of duodenal CCK cells are significantly lower in patients with IBS-D.	69
GIP	2015	The GIP cell density is significantly reduced in IBS-C.	69
GLP-1	2009	GLP-1 analog (ROSE-010) relieves acute pain attacks in IBS patients.	76
	2012	GLP-1 analog (ROSE-010) delays gastric emptying of solids in IBS-C patients.	75
	2014	Exogenous glucagon-like peptide 1 reduces contractions in human colon circular muscle.	72
	2017	Decreased serum GLP-1 correlates with abdominal pain in patients with IBS-C	71
PYY	2010	The increased PYY is observed in IBS-C patients whose colonic transit is delayed.	80
	2014	The expression of PYY is increased in the ileum in patients with IBS-C.	79
		The densities of PYY cells is significantly lower in IBS patients than controls.	81
		PYY expression is higher in the colon in post-infectious IBS.	82
	2017	PYY cell density is increased in IBS-C relative to controls.	94
Serotonin (5-HT)	2003	Plasma serotonin levels is increased in IBS-D.	91
	2006	Postprandial plasma serotonin level is decreased in IBS-C.	90
	2007	IBS patients have elevated concentrations of platelet depleted plasma 5-HT under fasting and fed conditions compared with controls.	87
	2009	Fasting and postprandial plasma 5-HT concentrations are significantly higher in IBS patients.	86
	2010	In the IBS samples, higher 5-HT content and lower SERT mRNA are detected as compared with controls.	179
		Post-infectious IBS patients have significantly lower plasma 5-HIAA.	70
	2011	Compared with healthy controls, patients with IBS show a significant increase in 5-HT-positive cell counts and 5-HT release.	92
	2012	The frequency of SLC6A4-polymorphism and higher levels of 5-HT are significantly associated with IBS	180
		Serotonin and PYY cell densities are reduced in the colon of IBS patients.	181
	2014	The intensity of serotonin transporter immunoreactivity is increased in the ileum of patients with IBS.	182
		The density of the serotonin-immunoreactive cells is significantly decreased in the IBS-M patients and increased in the IBS-C patients relative to the controls.	93
	2016	The 5-HIAA concentrations and 5-HT acetic acid /5-HT ratio are significantly lower in IBS compared to HC.	88
	2017	The densities of serotonin cells are reduced in IBS patients.	94
		IBS patients show increased 5-HT compared to healthy volunteers.	85

IBS, irritable bowel syndrome; IBS-D, irritable bowel syndrome with diarrhea; IBS-C, irritable bowel syndrome with constipation; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide; GLP-1, glucagon-like peptide 1; PYY, peptide YY; 5-HT, 5-hydroxytryptamine; SERT, serotonin reuptake transporter; 5-HIAA, 5-hydroxyindole acetic acid.

Motilin and ghrelin, which may accelerate gastric emptying, are potential pathogenetic factors targets for clinical management of FD. For instance, although fasting motilin levels in FD patients do not differ from those in healthy subjects, exogenous motilin stimulation produces greater inhibition of proximal gastric accommodation in FD patients.[36] In connection with gastric emptying, mitemcinal (a motilin receptor agonist) and ABT-229 (a motilin agonist) have been administered to patients with gastroparesis or FD, but it is still unclear whether they relieve symptoms such as abdominal satiety and pain in patients with FD.[37,38] Another motilin receptor agonist (camicinal; GSK962040) has been developed and used in a phase II trial for critically ill patients with food intolerance.[39] Camicinal has been shown to accelerate gastric emptying by 35-60% in patients with gastroparesis,[40] and therefore further clinical studies of

camicinal may be justified in patients with FD.

As for ghrelin, a few studies have reported that the level of ghrelin in plasma is decreased in FD patients,[41,42] whereas others have indicated that it is elevated in such patients and related to the severity of their symptoms,[43,44] and thus opinion is still divided. The plasma ghrelin concentration may decrease in accordance with the progression of gastric atrophy due to *Helicobacter pylori* infection.[45] In addition to gastric atrophy, obesity and stress also affect the plasma ghrelin level, thus complicating our understanding of how ghrelin is involved in the pathophysiology of FD. Ghrelin may be a potentially promising therapeutic agent for FD, and Akamizu et al[46] have reported that ghrelin administration improves appetite in affected patients. However, as their study was preliminary and did not include a placebo group, further large scale clinical studies including FD symptoms and GI motility assessments will be needed.

In patients with FD, both fasting and postprandial plasma CCK concentrations are higher. Interestingly, intake of a high-fat diet increases the CCK level significantly and is related to the severity of nausea, suggesting that fat diet-associated CCK is involved in the development of FD symptoms.[47] Furthermore, Chua et al[48] have reported that FD patients stimulated with CCK-8 showed more severe symptoms of dyspepsia than healthy controls, suggesting that FD patients are hypersensitive to CCK stimulation. Also, as CCK promotes serotonin secretion in the hypothalamus,[49] FD patients likely have central nervous system hypersensitivity to serotonin.[50] Thus, postprandial CCK may affect serotonin signaling in the central nervous system in FD patients and participate in the development of their symptoms.

The hormone incretin plays a role in not only postprandial glucose metabolism but also GI motility, strongly suggesting significant involvement of incretin in the food-intake-associated pathophysiology of FD. Although the fasting plasma GIP and GLP-1 concentrations do not differ between FD patients and healthy controls, FD patients show hypersensitive responses to lipid infusion into the duodenum.[51] Moreover, FD patients with severe symptoms show higher GIP and GLP-1 levels in response to lipid stimulation, supporting the contention that incretin mediates increased intestinal sensitivity to nutrients in FD. Witte et al[52] have also reported that although the GLP-1 concentration is altered in FD, postprandial GLP-1 secretion correlates with nausea in affected patients. GIP and GLP-1 may be important targets for the treatment of not only diabetes/metabolic syndrome but also FD, and therefore further clinical studies should be encouraged.

PYY as well as GLP-1 is known to act as an "ileal brake" by suppressing GI motility, implying its pathophysiologic involvement in FD. In this connection, it is tempting to speculate that plasma PYY might be increased in FD patients. However, Pilichiewicz et al[47] have reported that both the fasting and postprandial PYY levels are lower in FD patients than in healthy subjects, and Bharucha et al[51] have found no difference between the two. Thus, although plasma PYY is not increased in patients with FD, this issue requires further investigation.

Data on 5-HT abnormalities are relatively fewer for FD than for IBS patients. It has been reported that 5-HT_4 receptor agonists may improve symptoms of dyspepsia, particularly in patients with delayed gastric emptying.[53] Previous studies have shown that *5-HT receptor 3A* polymorphism[54] and *SERT* gene polymorphism are associated with dyspeptic symptoms.[55] Cheung et al[56] recently showed that low levels of baseline and postprandial 5-HT are associated with early satiation, lower calorie intake, and more severe postprandial dyspeptic symptoms in FD patients.

Irritable bowel syndrome

Irritable bowel syndrome (IBS) is characterized by symptoms such as abdominal pain or discomfort, bloating, and stool irregularities, without any structural or organic lesions.[57] Many factors are involved in the pathogenesis of IBS, and indeed gut hormones are key players, as described below.

The levels of motilin reported in IBS patients have been conflicting, various studies indicating that they are higher,[58] similar to,[59] or reduced[60] in comparison with healthy controls. Although dysmotility and visceral hypersensitivity are thought to play a crucial role in the pathophysiology of IBS, a high level of motilin may not reflect alteration of GI motility in IBS patients.[61] In addition, exogenous motilin does not affect rectal sensation, at least in healthy volunteers.[62] These findings suggest that alterations of the motilin level may be a consequence rather than a cause of IBS. The effect of erythromycin (a motilin receptor agonist) on colonic motility is also controversial; some studies have demonstrated that erythromycin accelerates the intestinal and/or colonic transit time,[63,64] whereas others have not confirmed this.[64,65]

It is interesting that the ghrelin cell density in the gastric oxyntic mucosa is altered in patients with IBS. On the other hand, since IBS and FD frequently overlap, it is not unlikely that endocrine cells may be altered in the upper GI in IBS. Although evidence is still insufficient, it has been reported that ghrelin cell density is decreased in patients with IBS with constipation (IBS-C).[66] This finding may not be surprising because the delay in intestinal transit time can be explained by inhibition of motility-promoting ghrelin. In contrast, ghrelin-positive cells are increased in patients with IBS

with diarrhea (IBS-D),[66] supporting the fact that such patients show rapid gastric emptying.[67] However, gastric emptying in IBS is still controversial.[68]

El-Salhy M et al[69] have shown that the densities of CCK are reduced in the duodenum of IBS-D patients, whereas they are not altered in IBS-C patients. In IBS-D patients, reduction of CCK may be involved in the rapid gastric emptying.[67] A subgroup of IBS patients are known to have a history of infectious colitis, and show an increased number of CCK-positive cells.[70] Furthermore, the plasma level of CCK is likely increased in the fasting and postprandial periods in IBS patients,[70] similarly to the situation in FD patients.[47] In contrast to the stomach, CCK stimulates intestinal motility, and therefore high CCK levels may be associated with the diarrhea seen in post-infectious IBS.

The density of duodenal endocrine cells differs between healthy controls and IBS patients. Indeed, GIP cell density is significantly decreased in both IBS-C and IBS-D,[69] but other information on GIP in IBS is sparse. Clinical trials of a GLP-1 analog have been performed in IBS patients. Li et al[71] have shown that the serum GLP-1 level was significantly decreased in IBS-C patients and negatively correlated with the severity of abdominal pain/discomfort. However, this seems paradoxical because GLP-1 inhibits intestinal motility and reduction of GLP-1 would lead to acceleration of GI motility. In this connection, opinion regarding the action of GLP-1 on colonic motility is still divided, both inhibitory and stimulatory effects having been reported.[72-74] In a placebo-controlled trial, Camilleri et al[75] showed that a GLP-1 receptor agonist, ROSE-010, improved colonic transit time in IBS-C patients, and Hellström et al[76] found that ROSE-010 administration relieved acute pain in patients with IBS. Additionally, the GLP-1 receptor agonist also decreases visceral sensitivity and accelerates colonic transit via the central corticotropin-releasing factor and peripheral vagal pathways, although these findings were obtained in animal experiments.[77,78]

The expression of PYY is increased in the ileum of patients with IBS-C.[79] As PYY inhibits colonic transit, it seems logical that IBS-C patients with delayed colonic transit show increased expression of PYY.[80] However, the number of PYY-positive endocrine cells is smaller in the colon and rectum in both IBS-D and IBS-C patients,[79,81] and PYY expression is high in the colon of patients with post-infectious IBS.[82] These discrepancies may reflect the complicated pathophysiology of IBS. In fact, it is known that IBS patients switch from one subtype to another at least once yearly,[83,84] probably as a result of the complex behavior of their enteroendocrine cells.

Data on 5-HT in IBS patients have been conflicting (Table 2). Some studies have reported that in both fasting and postprandial states, the plasma 5-HT level is increased in IBS patients relative to healthy volunteers,[85-87] whereas others have found no differences in the plasma 5-HT level between the 2 groups.[88] When IBS patients are subdivided, the plasma serotonin level is decreased in those with IBS-C[89,90] and increased in those with IBS-D.[90,91] A few histological studies have demonstrated that the number of 5-HT-positive cells is increased in IBS (especially post-infectious IBS),[89,92] although conflicting data have also been reported.[93,94] Genetic analyses of SERT polymorphism have also yielded mixed results.[95-97] However, such discrepancies are not surprising because 5-HT is not the only factor operating in the development of IBS. On the other hand, the receptors for 5-HT are widely expressed in various types of cells including neurons and smooth muscle cells,[35] and indeed 5-HT signaling is involved in GI motility and the development of IBS-related symptoms. In this context, it is noteworthy that release of 5-HT from the colonic mucosa correlated with the severity of abdominal pain in IBS patients.[92]

Role of Gut Microbiota in the Pathophysiology of Functional Gastrointestinal Disorders

The human microbiota comprises approximately 1200 different bacterial species whose number (10^{13}-10^{14}) in the gut is 10 times greater than the total number of cells in the human body.[2] Gut microbiota exert a marked influence on host physiology including metabolism, nutrition, and immune function, and therefore, its disruption or alteration has been linked with GI inflammatory and functional disease.[98] It has become increasingly evident that host-gut microbial interactions have an extremely important role in the pathogenesis of FGIDs (Table 4), especially IBS.[99] Recent advances in sequencing technology have revealed that the profile of gut microbiota differs between patients with IBS and healthy subjects, and this has promoted researchers to investigate the role of the gut microbiota in IBS.

Gut Microbiota Production of Serotonin and SCFA

Evolutionarily-oriented studies have shown that many enzymes involved in human hormone metabolism have evolved through gene transfer from bacteria.[100] Interestingly, serotonin and other hormones such as epinephrine, norepinephrine and dopamine are produced and/or secreted from specific bacterial strains.[101] Furthermore, it has been revealed that microorganisms harbor hormone receptors,[102] suggesting that gut hormones act as possible mediators

of communication between the host and gut microbiota.

Depending on the substrates (amino acids, lipids or carbohydrates) present in the intestinal lumen, gut microbiota can generate specific metabolites. Short-chain fatty acids (SCFAs) are produced by microbiota in the ileum and colon from carbohydrates with low digestibility (resistant starch and soluble oligo- and polysaccharides). The main components of SCFAs in the human colon are acetate (2-carbon), propionate (3-carbon), and butyrate (4-carbon), at a ratio of about 3:1:1.[103,104] Butyrate is considered a major energy source for the colonic epithelium. Propionate, entering the portal circle, is primarily utilized for gluconeogenesis in the liver. Consequently, SCFAs in plasma are largely acetate.[105,106] Approximately 95% of the produced SCFAs are rapidly absorbed by colonocytes in the large intestine while the remaining 5% are secreted in the stools.[107]

Short-chain Fatty Acids as a Mediator between Gut Microbiota and Endocrine Cells

SCFAs serve as not only an important energy source but also chemical messengers or signaling molecules for various types of cells. GPR41 and GPR43, which are classified as G protein-coupled receptors and known as free fatty acid receptor (FFAR)3 and FFAR2, respectively, have recently been identified as receptors for SCFAs. Since these receptors are expressed in a variety of cell types, including colonic endocrine L cells, mucosal mast cells, adipose tissue, neutrophils, and monocytes, activation of these receptors may elicit distinct functions in various fields. Both GPR41 and GPR43 exhibit coupling to the Gi/o family and inhibit cAMP production, whereas GPR43, but not GPR41, also couples efficiently through the Gq protein family.[108]

In the ileum and colon, GPR41 and GPR43 are expressed in enteroendocrine L-cells that secrete GLP-1 and PYY.[109] Therefore, it had been expected that SCFA would promote GLP-1 and PYY secretion by activating these GPRs, and indeed several in vivo studies have demonstrated that intraluminal injection of SCFAs induced the release of PYY and GLP-1 into the circulating blood.[110] Furthermore, in vitro studies have shown that activation of GPR43 by SCFAs promotes GLP-1 secretion[111] and PYY expression[112] in enteroendocrine cells. On the other hand, individual GPR41- or GPR43-deficient mice show low GLP-1 release in response to SCFA stimulation, indicating that both GPR41 and GPR43 are involved in SCFA-evoked GLP-1 release.[111] These findings strongly suggest that SCFA signaling to GPR41 and GPR43 on L cells is crucial for controlling the levels of GLP-1 and PYY, thus playing a pivotal role in the "ileal brake." However, in GF mice, Wichmann et al[113] have demonstrated that total SCFA in the cecal content is decreased whereas the plasma GLP-1 level is increased. They showed that colonization of GF mice with microbiota or treatment with SCFAs reduced the expression of GLP-1 in the colon.[113] Although these findings are difficult to reconcile, the explanation proposed is that GF mice are deprived of SCFAs produced by gut microbiota and serve as an important energy source for colonocytes. Subsequently, in response to this insufficiency of available energy in the colon, the GLP-1 level is increased to slow intestinal transit. In this context, GPRs may act as sensors of the amount of SCFA rather than being receivers of SCFA signaling.

SCFAs may be involved in the production of not only GLP-1 and PYY, but also other gut hormones such as 5-HT, GIP, ghrelin, and CKK. Histological studies have clarified that GPR43 is co-expressed with 5-HT,[114] and that SCFAs stimulate the release of 5-HT by EC cells in the colonic mucosa.[115] On the other hand, GPR40 and/or GPR120 are co-localized in cells expressing GIP, GLP-1, PYY, CCK, ghrelin, or 5HT,[116-118] although their ligands are predominantly medium- to long-chain fatty acids.[119] Taken together, the available data suggest that GPRs are key tools involved in the interaction between endocrine cells and fatty acids produced from food and gut microbiota.

Alterations of Gut Microbiota in the Pathophysiology of Functional Gastrointestinal Disorders

The Rome Foundation has recently provided an excellent overview of the importance of microbiota in health and disease, especially functional bowel diseases.[99] It is widely accepted that GI infections caused by bacteria, viruses, or parasites are strong risk factors for the development of FGIDs.[120] With regard to the association between bacterial infection and FD, almost all current knowledge is based on *H. pylori* infection. *H. pylori* causes chronic atrophic gastritis, gastroduodenal ulcers and gastric cancers, suggesting a close involvement in the development of organic disease. In this context, whether or not patients with *H. pylori* infection should be excluded from the category of FD has been discussed. However, possible pathogenetic concepts to explain the link between *H. pylori* infection and dyspeptic symptoms have been positively incorporated into the recent Rome IV classification[121] and management guidelines for *H. pylori* infection.[122] In response to the recent focus on gut microbiota and FGIDs, several studies have begun to investigate the gastric microbiota in FD patients. For instance, as dysbiosis has been observed in the gastric fluid of patients with FD,[123] it has been suggested that normalization of the gastric microbiota by probiotics

Table 4. Data by Microbiota Analyses in Functional Gastrointestinal Disorders Patients

Published year	Main findings of microbiota analyses in FGID patients	Reference No.
Functional dyspepsia		
2016	The overall structure of the bacterial community and the abundance of genus Prevotella in the gastric fluid of the FD patients were significantly different from those in the HC.	123
2017	Alteration in the gastric fluid microbiota characterized by Bacteroidetes > Proteobacteria abundance and the absence of Acidobacteria was found in the gastric fluid of patients with FD.	124
Irritable bowel syndrome		
1994	IBS is frequently occurred in patients after Salmonella-induced enteritis.	125
2005	Lower amounts of *Lactobacillus* spp. were present in the samples of IBS-D patients whereas IBS-C patients carried increased amounts of *Veillonella* spp.	183
2007	Significant differences between IBS and control were found in several bacterial genera which belong to Coprococcus, Collinsella, and Coprobacillus.	184
2009	The microbial communities of IBS-D patients were enriched in Proteobacteria and Firmicutes, but reduced in the number of Actinobacteria and Bacteroidetes compared to HC.	185
2010	IBS patients showed significantly higher counts of *Veillonella* and *Lactobacillus* than controls.	186
	A significant difference between IBS and HC was indicated with significantly more variation in the gut microbiota of healthy volunteers than that of IBS patients.	187
	Quantitative PCR analysis demonstrated a significant 3.6 fold increase in concentrations of fecal *Lactobacillus* species between IBS-D patients and HC.	188
2011	Pseudomonas aeruginosa was significantly more abundant in faeces of IBS patients than in faeces of healthy subjects.	189
	The microbiota of IBS had a 2-fold increased ratio of the Firmicutes to Bacteroidetes compared with controls.	130
	Microbiomes associated with pediatric IBS were characterized by a significantly greater percentage of the class γ-proteobacteria; one prominent component of this group was Haemophilus parainfluenzae.	190
	The biodiversity of microbes within fecal samples from IBS-D patients is lower (1.2-fold) than that from HC.	191
2012	IBS microbiota showed an increase in relative abundance of lactobacilli, *B. cereus* and *B. clausii*, bifidobacteria, *Clostridium* cluster IX and *E. rectale*, and a decrease in abundance of Bacteroides/Prevotella group and Veillonella genus.	192
	IBS-D patients had significantly higher levels of Enterobacteriaceae and lower levels of Fecalibacterium genera compared to HC.	193
	An increased Firmicutes:Bacteroidetes ratio best characterises those IBS subjects who differ from normal populations.	194
	Bifidobacteria were lower in the IBS-D group than in the IBS-C group and controls. The maximum number of stools per day negatively correlated with the number of mucosa-associated Bifidobacteria and Lactobacilli in IBS.	195
2013	The sensitivity to colonic distension of IBS patients can be transferred to rats by the fecal microbiota.	131
2014	Several members of Bacteroidetes phylum were increased 12-fold in PI-IBS patients, while HC had 35-fold more uncultured Clostridia.	196

Table 4. Continued

Published year	Main findings of microbiota analyses in FGID patients	Reference No.
2015	Differences in the mucosal-associated microbiota between healthy individuals and IBS patients are minimal (one bacterial group) compared to differences in the faecal microbiota of both groups (53 bacterial groups).	197
	Validation confirms dysbiosis was detected in 73% of IBS patients, 70% of treatment-naïve IBD patients and 80% of IBD patients in remission, vs. 16% of healthy individuals.	198
	16S rDNA sequencing confirmed microbial overgrowth and its diversity-reduction in the small bowel of IBS patients.	199
	Number of Bacteroides thetaiotamicron and Pseudomonas aeruginosa were higher among IBS patients. Number of Bacteroides thetaiotamicron and segmented filamentous bacteria (SFB) was higher among IBS-D than IBS-C. Abdominal distension was associated with higher number of *Bacteroides thetaiotamicron*, *Clostridium coccoides*, *P. aeruginosa*, SFB, and Gram-negative bacteria (GNB); bloating was associated with *Clostridium coccoides* and GNB.	200
	Fecal microbiota composition of PI-IBS patients differed significantly from both general IBS patients and HC. Both mucosal and fecal microbial diversity were reduced in PI-IBS compared to HC.	201
2016	Higher abundance of colonic Veillonellaceae and small intestinal Prevotellaceae, and lower amount of oral cavity normal flora in proximal small intestine were found in IBS patients.	202
	Bacteroidetes was predominant in fecal samples from HC and IBS-D and IBS-M subjects, whereas Firmicutes was predominant in samples from IBS-C subjects. Species richness, but not community diversity, differentiated all IBS patients from HC.	203
	In IBS-C patients, Bacteroides, Roseburia-Eubacterium rectale and Bifidobacterium were decreased, and Enterobacteriaceae, Desulfovibrio sp., and mainly Akkermansia muciniphila were increased compared to healthy individuals.	204
2017	Mice receiving the IBS-D fecal microbiota, exhibited faster gastrointestinal transit, intestinal barrier dysfunction, innate immune activation, and anxiety-like behavior.	205
	Down-regulation of bacterial colonization including *Lactobacillus*, *Bifidobacterium*, and *F. prausnitzii* was observed in IBS patients, particularly in IBS-D.	206
	IBS symptom severity was associated negatively with microbial richness, exhaled CH4, presence of methanogens, and enterotypes enriched with Clostridiales or Prevotella species.	207
	Compared with healthy controls, the standardized mean differences of Bifidobacteria, *Lactobacillus*, *Escherichia Coli*, and *Enterobacter* were significant in Chinese IBS patients.	208
	Using linear discriminant analysis effect size method, gut dysbiosis was observed in subjects with IBS (Plesiomonas and Trabulsiella, effect size 3.0).	209
2018	The fecal microbiota dysbiosis was more prevalent in IBS than in healthy volunteers.	210
	FMT significantly relives the symptom in IBS patients.	211
	In IBS, *Dialister* spp. and *Faecalibacterium prausnitzii* were the most representative species.	212

FGID, functional gastrointestinal disorders; HC, healthy controls; FD, functional dyspepsia; IBS, irritable bowel syndrome; IBS-D, IBS with diarrhea; IBS-C, IBS with constipation; PCR, polymerase chain reaction; IBS-M, mixed IBS; PI-IBS, post-infectious IBS; FMT, fecal microbiota transplantation.

might be an effective treatment.[124] However, studies of the gastric microbiota in FGIDs are still at an early stage.

The link between GI infection and FGIDs has been studied mainly in IBS. In 1994, a group in the United Kingdom reported that IBS frequently occurs in patients after *Salmonella*-induced enteritis.[125] Thereafter, similar observations were reported worldwide, and a recent meta-analysis has clearly shown that IBS occurs frequently after bacterial enteritis caused by pathogenic strains of *Escherichia coli*, *Salmonella*, and *Campylobacter jejuni*.[126] Moreover, it is interesting that FD also occurs frequently in patients after bacterial enteritis, being compatible with the fact that IBS and FD often overlap in a single patient.[126] After remission of bacterial enteritis, no endoscopic and/or microscopic abnormalities are detectable in the GI tract of such FGID patients. Why, then, do patients with post-infectious IBS show visceral hypersensitivity and GI dysmotility? Accumulating evidence has led to a hypothesis that pathogens disrupt the mucosal barrier and that subsequently mucosal immune cells are persistently activated as a result of increased exposure to luminal antigens.[127] This low-grade mucosal inflammation is able to affect the immune system, endocrine cell behavior, and subsequently visceral sensitivity and GI motility. This modification of the gut environment may be central to the development of post-infectious IBS.

As only about 10% of IBS patients have a history of infectious colitis,[128] what is the role of gut microbiota in IBS patients without such a history? Recent advances in sequencing technology have made it easier to obtain information on gut microbiota at the genus level. Comprehensive analyses of fecal samples have demonstrated that the gut microbiota profile in IBS patients is largely different from that in healthy subjects, and has reduced diversity.[99,129] Specifically, several studies have demonstrated increased *Firmicutes* to *Bacteroidetes* ratios at the phylum level in IBS patients.[99,129,130] At the genus level, *Lactobacillus*, *Bifidobacterium* and uncultured *Clostridium* are decreased in patients with IBS, whereas *Ruminococcus* species are enriched.[130] Although it seems impossible to determine which bacterial strain is responsible for the development of IBS, dysbiosis of the microbiota is definitely a contributing factor. This is supported by experimental evidence that germ-free (GF) animals given microbiota transplants from IBS patients show visceral hypersensitivity and GI dysmotility.[131,132] On the other hand, although stress events in early life are closely associated with IBS development, the gut microbiota profile may be possibly modified by such events.[133,134] Moreover, antibiotic-induced dysbiosis (especially in childhood) has also been shown to be involved in the development of IBS.[133,135] These findings suggest that events in early life may be crucial in determining the IBS-related profile of gut microbiota. This invites speculation that manipulation of the gut microbiota may be useful for the treatment of IBS. Interestingly, the antibiotic rifaximin has been demonstrated to relieve the symptoms of IBS,[136] although the mechanism responsible remains unclear. A meta-analysis has also indicated that probiotics may reduce IBS symptoms, although there was significant heterogeneity among the studies investigated,[129,137,138] and the mechanism through which such probiotics act remains to be elucidated.

Possible Axis of Gut Microbiota and Enteroendocrine System Interaction in Functional Gastrointestinal Disorders Dysmotility

FGIDs are diagnosed on the basis of characteristic symptoms that are closely associated with food intake. The pathogenesis of FGIDs is multifactorial, and includes the neuroendocrine system, gut microbiota, neuroimmune reactions, interactions, psychological factors, and dietary factors.[129] The complexity of FGID pathophysiology may be due to the fact that through their interaction, these factors may become a cause and/or a consequence of the pathophysiology. The physiological alterations in FGIDs are also complicated, but there is little doubt that GI dysmotility and visceral hypersensitivity are critical. Here, we would like to focus on the interrelationships existing among gut microbiota, gut hormones and GI dysmotility in FGIDs (Figure).

Enteric Nervous System Receptors

The enteric nervous system (ENS) in the GI tract comprises a network of 200-600 million neurons and is involved in multiple aspects of host physiology including motility, metabolism, and behavior. This neural network is arranged in distinct units between the longitudinal and circular muscle layers of the intestine or in the submucosa as ganglionated plexi.[139] Gut microbiota may interact with the ENS directly or via afferent nerves (vagal sensory neurons, spinal sensory neurons and intrinsic primary afferent neurons) and the CNS indirectly through neurotransmitters. The link between microbiota and the ENS has been demonstrated in GF mice, which show a reduced number of enteric neurons and associated deficits of gut motility,[140] whereas reconstitution of GF mice with conventional microbiota normalizes the density of the ENS network and, subsequently, gut physiology.[141]

How, then, does the gut microbiota affect the ENS? Importantly, the ENS expresses pattern recognition receptors known as

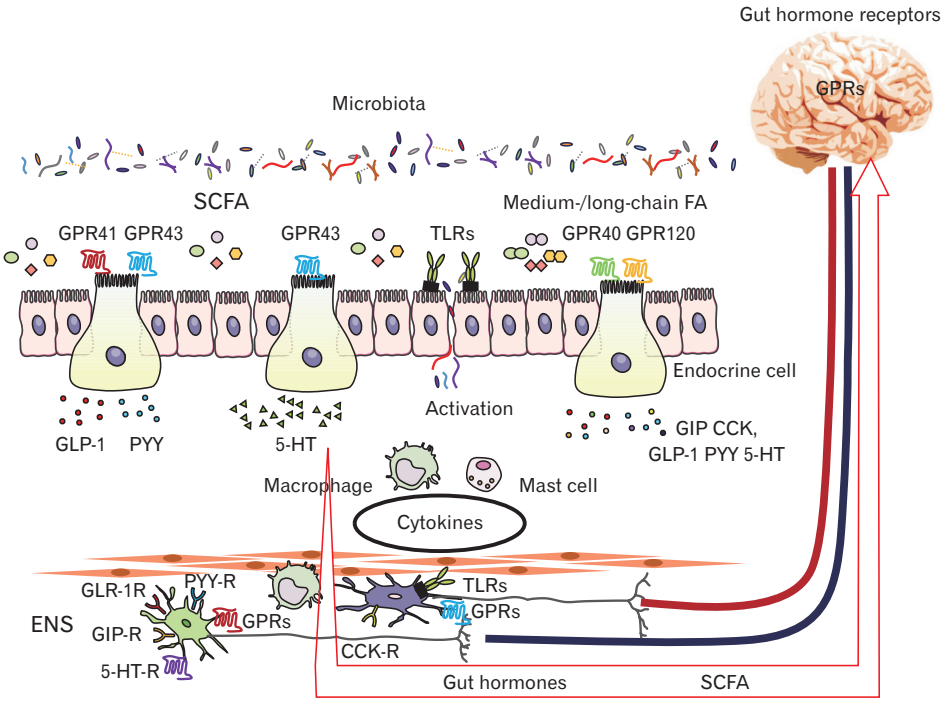

Figure. Interaction among gut microbiota, enteroendocrine cells, immune cells, and enteric nervous system (ENS). SCFA, short-chain fatty acid; FA, fatty acid; GPR, G protein-coupled receptor; TLR, toll-like receptor; GLP-1, glucagon-like peptide 1; PYY, peptide YY; 5-HT, 5-hydroxytryptamine; CCK, cholecystokinin; GIP, glucose-dependent insulinotropic polypeptide/gastric inhibitory polypeptide; -R, receptor.

Toll-like receptors (TLRs) by which the microbiota communicate with the host.[142] Anitha et al[140] have demonstrated that *TLR4*-deficient mice show a significant decrease of both the ENS network and GI transit time, and similar findings have been observed in *TLR2*-deficient mice.[143] Another important ENS receptor type are the GPRs such as GPR41 and GPR43, which respond to SCFA signaling. Since the gut microbiota produce SCFAs, they can use them as chemical messengers or signaling molecules to communicate with the host ENS. At present, although little is known about a molecular alteration of the ENS by SCFA stimulation, treatment with butyrate enhances histone H3 acetylation in enteric neurons and increases the contraction of cholinergic-mediated colonic circular muscle.[144]

Gut Microbiota, Immune System Activation, and Gastrointestinal Motility

Not only the direct but also the indirect action of gut microbiota on the ENS is important, and this interaction is complicated. Microbiota-derived SCFAs play roles in the maintenance of intestinal barrier function,[145,146] and indeed, butyrate, a microbiota-derived SCFA, prevents bacterial translocation by increasing the expression of tight junction proteins such as claudin, occludin, and the zonula occludens.[147] In this context, it is interesting to note that in IBS patients butyrate-producing bacteria may be reduced[148] and intestinal permeability is increased.[149,150] Thus, leakage of pathogens into the lamina propria of the intestinal mucosa is a significant trigger for activation of the mucosal immune system. In IBS patients, increased amounts of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6, and IL-8) and decreased amounts of the anti-inflammatory IL-10 have been reported.[151] Th1 cytokines such as TNFα, IL-1β, and IL-6 may act on the ENS and smooth muscle, resulting in suppression of GI motility.[152,153] On the other hand, Th2 cytokines including IL-10 may inhibit the expression of the above cytokines, thus accelerating of GI motility.[152,154] In IBS, it is still unclear whether these cytokines simply show this pattern of interaction. However, imbalance of not only gut microbiota but also the cytokine profile must be associated with intestinal low-grade inflammation, which is a significant pathophysiologic alteration in IBS.

Among the various immune cells, mast cells have been highlighted in the pathophysiology of IBS as their numbers are increased in colonic tissues of affected patients, and this increase is correlated with the severity of the clinical symptoms.[155,156] Mast cells are able to release histamine, serotonin, tryptase, and prostaglandins, and these mediators may act on their specific receptors on myenteric neural cells, leading to altered motor function.[155] Recent evidence has emphasized the pivotal roles of macrophages in GI motility through their action on myenteric neural cells,[152,153,157,158] and indeed increased infiltration of macrophages into colonic tissues is observed in IBS patients,[156,159] implying that macrophages, like mast cells, may affect the ENS and smooth muscle through various

mediators.[152,153,157,158] Recently, macrophages have been classified into the M1 and M2 types that produce mainly Th1 and Th2 cytokines, respectively.[160,161] Thus, M1 macrophages release proinflammatory cytokines such as TNFα, IL-1β, and IL-6, whereas M2 macrophages may suppress M1 macrophages by releasing anti-inflammatory cytokines. Interestingly, M2 macrophages are known to infiltrate into the muscle layer of the intestine and may accelerate GI motility through stimulation with Th2 cytokines.[155] Furthermore, it has been reported that serotonin plays a role in polarization of macrophages toward an M2 phenotype.[160,162] Supporting these findings, we have clarified that 5-HT expression is increased in the colon of GF mice after fecal transplantation, and that moreover M2 macrophages in the colonic muscular layer are increased in those mice.[163] Furthermore, it is noteworthy that the numbers of muscularis M2 macrophages and 5-HT-positive endocrine cells are significantly correlated throughout the GI tract, and that their increase is associated with acceleration of GI motility. Thus, the gut microbiota plays a role in the association between accelerated GI motility and induction of the 5 HT/muscularis mannose receptor positive macrophage axis in the GI tract.[163] Specifically, Muller et al[164] have demonstrated that M2 macrophages migrating adjacent to the ENS may be involved in the control of GI motility through cross-talk with enteric neurons via bone morphogenetic protein 2 signaling.

Gut Microbiota and Gastrointestinal Motility-associated Hormones

The gut microbiota is able to affect GI motility via gut hormones. As shown in Tables 2 and 3, many investigators have intensively studied the gut microbiota and 5-HT in patients with IBS. However, to clarify the role of gut microbiota in the gut hormone/GI motility axis in IBS, experimental animal studies are needed. In particular, much evidence has been obtained from experiments using GF animals. For example, Wikoff et al[165] first demonstrated that GF mice display lower levels of 5-HT than conventionally raised animals, suggesting that the presence of gut microbiota is essential for the production and release of 5-HT.[165] In addition, Kashyap et al[166] have clarified that colonization of GF mice with gut microbiota from humans or mice can significantly shorten the GI transit time and that this effect is partially inhibited by 5-HT receptor antagonist.[166] These findings strongly indicate that 5-HT induced by microbiota stimuli play a role in the acceleration of GI motility. Moreover, Yano et al[167] have clarified that indigenous spore-forming bacteria from the gut microbiota promote tryptophan hydroxylase 1 expression and 5-HT biosynthesis in EC cells, thus modulating GI motility. Although the mechanism by which microbiota induce 5-HT expression is still unclear, SCFA and cytokines in minimal inflammation may be candidate stimuli for 5-HT-producing EC cells,[168] and the microbiota themselves may also produce 5-HT.[101] On the other hand, various types of 5-HT receptors are present on not only central and peripheral neural cells but also immune cells, smooth muscle, and enterocytes.[168,169] Additionally, the SERT, which terminates the action of 5-HT, is expressed in epithelial cells, neural cells, and platelets.[169] Accordingly, it is extremely difficult to determine how the gut microbiota/5-HT axis operates in GI motility and the development of symptoms in FGIDs.

Recently, not only 5-HT but also other gut hormones have been highlighted in relation to the gut microbiota/gut hormone axis in GI motility. As a result of their elegant work, Wichmann et al[113] have proposed that the microbiota/GLP-1 axis is important for regulation of energy availability and GI motility. Specifically, enteroendocrine L cells sense the amount of bacteria-producing SCFA in the colon and secrete GLP-1 to allow greater nutrient absorption by inhibiting intestinal motility. Accordingly, it is tempting to speculate that GPR41 and GPR43 may play some roles in this process because these receptors are responsive to SCFA ligands. In support of this hypothesis, in vitro studies have shown that the SCFA affects GLP-1 secretion via GPR43 and/or GPR41 in L cells.[111,170] Enteroendocrine cells are significant intermediates in facilitating communication between microbes and the ENS.[171] By using GF with fecal transplantation animal models, we have recently demonstrated that gut microbiota accelerate GI motility while suppressing the expression of the GLP-1 receptor in myenteric neural cells throughout the GI tract.[172] These findings suggest that the gut microbiota affects the expression of gut hormone receptors on the ENS in the GI muscle layer.

Except for 5-HT and GLP-1, there are few data on the role of the gut microbiota/gut hormone axis in GI motility. As PYY is produced in L cells, it may—like GLP-1—be a sensor for SCFA and inhibit GI motility. Interestingly, GPRs are widely expressed in enteroendocrine cells such as those producing ghrelin, CCK, GIP, PYY, or GLP-1.[170] Moreover, since enteric neurons harbor the receptors for all of these gut hormones, a mechanism similar to that for GLP-1 or 5-HT may exist in the microbiota/gut hormone axis to mediate GI motility.

Summary and Conclusions

Gut microbiota have a pivotal influence on various functions including GI motility, metabolism, nutrition, immunity, and the

neuroendocrine system in the host. This variety of bacterial actions is due to the production of SCFA and various mediators such as gut hormones and/or cytokines, which gut microbiota induce in enteroendocrine and immune cells. Moreover, the receptors for SCFA and gut hormones are widely distributed in neural cells, endocrine cells, immune cells and smooth muscle, further making it difficult to understand the role of gut microbiota in the pathophysiology of FGIDs. GI motility is well orchestrated by the ENS and hormonal networks, and its disturbance is closely associated with not only GI dysmotility but also visceral hypersensitivity and energy imbalance, that are significant abnormalities in the pathophysiology of FGIDs. In this article, we have mentioned that the gut microbiota may affect the ENS directly via the SCFA, or indirectly via gut hormones. Furthermore, we have described that gut microbiota elicit minimal inflammation by activation of the immune system and that mast cells and macrophages modify GI motility by acting on the ENS and smooth muscle. In this context, alteration of the gut microbiota/gut hormone axis significantly affects GI motility in the pathophysiology of FGIDs.

Although we have focused on GI motility in FGIDs, both the gut microbiota and gut hormones also play pivotal roles in metabolism, the brain-gut axis, and systemic immunity. Interestingly, the gut microbiota and gut hormones have been highlighted as targets of new therapeutic approaches for FGIDs, and indeed some trials using probiotics, antibiotics or gut hormone agonist/antagonists have been undertaken. Also, fecal microbiota transplantation, as applied to *Clostridium difficile* infection, may be attempted for FGIDs in the future. The research field focusing on interactions between gut microbiota and gut hormones may be referred to as "microbial endocrinology," and is expected to become a focus of intense interest in the near future.

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