The Cutting Edge Research of Functional Gastrointestinal Disorders in Japan: Review on JGA Core Symposium 2018–2020

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Abstract

Highly impacted articles on functional gastrointestinal (GI) disorders research presented at the core symposium held in the Japanese Gastroenterological Association (JGA) annual meeting 2018–2020 are selected and summarized. Regarding visceral hypersensitivity and sensor in GI tracts, transient receptor potential vanilloid 4 ion channel and acid-sensitive ion channel were candidates for hypersensitivity in GI tracts. ATP release from vesicular nucleotide transporter may be a key pathway to sensitize the nerve endings. Regarding inflammation and mucosal immune responses, patients infected with *H. pylori* having Ser70 type single nucleotide polymorphism of NapA gene was associated with *H. pylori*-related dyspepsia via gastric dysmotility. Gastric histology infected with Ser70 type NapA was shown severe infiltration of neutrophils into intramuscular layer. Macrophages, mast cells, and neutrophils are infiltrated in the colon of irritable bowel syndrome (IBS) patients and the locally produced IL-1 β upregulated brain-derived neurotrophic factor (BDNF) in

enteric glia cells. BDNF can also stimulate nerve endings and might be linked to pain in the colon. Dysbiosis in the composition of commensal bacteria communities is associated with the pathogenesis of various diseases including IBS and gut-brain interaction. The investigation on the mucosa-associated microbiota (MAM) is essential for understanding the interactions. The α -diversity and β -diversity of MAM indices are significantly different among IBS-D, IBS-C, and controls, and the different diversity might contribute to the pathophysiology of IBS. As research works on psychosocial factors show, maternal separation animal model was used and it is early life stress. The stress had induced colonic hypercontraction, gastric hypersensitivity, and delayed emptying. The precise molecular mechanisms are still under investigations.

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Introduction

The scientific organizing committee of the Japanese Gastroenterological Association (JGA) has selected the updated topics as a core symposium, and the core symposiums were continuously held for 3 years in the annual meeting. During the annual meeting 2018–2020, the up-

Fig. 1. Biopsychosocial conceptual model of FGIDs. GI physiology and psychosocial factors are interacting on the onset of FGIDs. The key concept is gut-CNS/brain interaction. FGIDs, functional gastrointestinal disorders; GI, gastrointestinal; CNS, central nervous system.

dated research works on functional gastrointestinal disorders (FGIDs) were presented, especially focusing on the pathophysiology and the new diagnostic researches regarding gastroesophageal reflux diseases (GERDs), functional dyspepsia (FD), and irritable bowel syndrome (IBS). The Rome Foundation Committee revised the previous Rome III classification and criteria for FGIDs and had published a new Rome IV classification and criteria in 2016. FGIDs are recognized by physiological and morphological abnormalities combining with dysmotility, visceral hypersensitivity (aberrant perception), altered mucosal immune function, altered gut microbiota, and interaction with the central nervous system (CNS). The central biopsychological concept of Rome IV is the interaction between gut and CNS, gut-brain interaction as well as brain-gut interaction, vice versa (Fig. 1) [1]. Motility, sensation, immune dysfunction, microbiota, and food/diet are primarily included in gut side, while psychosocial factors with life stress, psychological status, personality, and social support are included in the CNS or brain side.

In this meeting review, highly impacted articles presented at the core symposium of JGA annual meeting 2018–2020 were selected and are introduced according to the central concept of FGIDs in Rome IV.

Visceral Hypersensitivity and Sensor in Gastrointestinal Tracts

The visceral hypersensitivity and the aberrant perception to mechanical stretch, temperature, and environmental factors in gastrointestinal (GI) tracts (gut microbiota, foods, mucosal inflammation, and others) plays a critical role in the outcome of FGIDs; however, the molecular basis is still unclear.

Transient receptor potential vanilloid 4 (TRPV4), one of the stretch-activated non-selective cation ion channel family, is one candidate to mediate the visceral hypersensitivity [2]. TRPV4 was originally identified as a hypo-osmolarity-sensitive ion channel that is activated by mechanical stimuli, warm temperature, and epoxyeicosatrienoic acid.

In the annual meeting 2018 and 2019, Mihara et al. [3] presented that TRPV4 and vesicular nucleotide transporter (VNUT) were expressed throughout GI epithelial cells [3–5] in mouse as well as in human. VNUT is responsible for vesicular ATP storage in ATP-secreting cells. The epithelial ATP releasing in response to luminal distension or stretch can act on ATP receptors in submucosal nerves and transduce a signaling to CNS or induce an enteric reflex. The stimulation of TRPV4 has induced ATP exocytosis from VNUT and led to ATP release. There are 2 types of ATP receptors, P2X family of ionotropic receptors and P2Y family of G protein-coupled receptors, and both are involved in visceral hypersensitivity [6]. For example, P2X3 agonist can stimulate mechanosensitive vagal afferent nerves in the stomach as well as the esophagus [7], suggesting that ATP release induced by mechanical stimuli and P2X3 receptor, both play also a role in baro-reception in GI tracts. Additionally, ATP released from enterobacteria, activated submucosal basophils, and mast cells can function to stimulate inhibitory nerves endings in gut. As TRPV4 itself are known to be upregulated in the inflamed GI mucosae; therefore, this stretch-activated nonselective cation ion channel family might be interacting with the inflammation and/or the mucosal immune systems in the gut.

In human esophagus epithelia cells, acid stimulation promotes ATP release [8] and could be linked to the hypersensitivity of GERDs, especially nonerosive GERDs. GI epithelial cells in the esophagus, stomach, and small intestine are releasing ATP in response to chemical, hypo-osmolality, temperature, stretch, and acid (Fig. 2) [5], and this pathway could have multi-functions in terms of visceral hypersensitivity in GI tracts. Recently, the first generation bisphosphate clodronate was shown to specifically inhibit VNUT activity at low concentration, sug-

Fig. 2. Proposed molecular mechanism of visceral hypersensitivity via TRPV4 as a sensor. TRPV4 expressed in GI epithelial cell is activated by stretch, heat, hypo-osmolality, LPS, or the endogenous activators (5,6-EET and 8,9-EET). Inflammation, altered mucosal immune response, and gut microbiota are modulating TRPV4 function. TRPV4 activation has induced VNUT-mediated ATP exocytosis and increases cellular permeability, and the ATP is stimulating the nerve endings in the gut. This figure is modified from [5]. GI, gastrointestinal; TRPV4, transient receptor potential vanilloid 4; VNUT, vesicular nucleotide transporter.

gesting that this compound could be an effective agent to treat chronic pain [9], possibly to relief the pain-related symptom in FGIDs.

In the annual meeting 2018, Kamiya et al. also reported that an acid-sensitive ion channel 5 (ASIC5) mRNA was expressed on the duodenal epithelial cells, and ASIC5 might function as a pain-related chemoreceptor or as a sensor to bile acid [10]. These observations may suggest that ASIC5 is related to the symptom with disorders of gallbladder and sphincter of Oddi in FGIDs.

Inflammation and Immune Response in Gut

H. pylori-related dyspepsia was newly defined in Rome IV classification and criteria. Although the contribution of eradication treatments to *H. pylori* in FD is not high in Western countries (around 10% in FD patients), *H. pylori*-related dyspepsia should be considered as 1 clinical subtype separated from classical FD. The introduction of this new subtype in FD has much contributed in Asian countries, including Japan, because the eradication effects were reported to be much higher in FD patients in these countries [11, 12].

Matsuzaki et al. reported in the annual meeting 2018 that the patients with *H. pylori*-related dyspepsia had restrictedly Ser70 type single nucleotide polymorphism (SNP) of NapA gene, which promotes neutrophil activation in *H. pylori*-infected gastric mucosae, and the patients infected with *H. pylori* having Ser70 type NapA SNPs demonstrated severe infiltration of neutrophils into intramuscular layer (Cajal pacemaker cells are localized), and these observations might be contributed to dysmotility of the stomach in patients with *H. pylori*-related dyspepsia.

In IBS, the SNPs of several genes are investigated that they have a linkage to IBS in a large-scale genome-wide study, and a cluster of 21 correlated SNPs has significant association with IBS [13]. These SNPs might be linked to gut-brain and brain-gut interactions. The researches on functional linkages and localization of the target genes will be required to understand the association with IBS.

Fukumoto et al. reported in the annual meeting 2019 that brain-derived neurotrophic factor (BDNF) was expressed in rat enteric glia cells (EGCs), and the expression was enhanced by IL-1 β stimulation in protein as well as mRNA levels with dose-dependent manner. As macrophages, mast cells and neutrophils are well known to be infiltrated in the colon of IBS patients, the local IL-1 β could be upregulated BDNF production in the colon. BDNF can also stimulate nerve endings and might be linked to pain in the colon. On the other hand, BDNFs are required for anti-depressant action in brain [14]. Although the precise mechanisms of BDNFs in CNS and gut are not fully investigated, BDNFs may be a key factor in terms of gut-brain interaction as well as brain-gut interaction.

Low-grade inflammation is considered to be an important factor in the pathogenesis of FGIDs. Elevated serum inflammatory cytokines, such as IL-6, IL-8, and TNF- α and decreased serum anti-inflammatory cytokines, such as IL-10, were detected in IBS patients, compared with healthy controls [15]. Further, the upregulated expression of inducible nitric oxide and IL-1 β are closely associated with the inflammation in patients with IBS-D [16].

On the other hand, immune reaction to food in the intestinal mucosa is also a crucial key factor in the pathogenesis, especially in patients with IBS-D. The relationship between IBS and food hypersensitivity currently has been researched. However, the prevalence of food hypersensitivity among IBS patients has not been investigated sufficiently, and its underlying mechanism remains unclear. Katsumata et al. [17] reported in the annual meet-

Fig. 3. β -diversity PCoA UniFrac analysis weight (a), unweight (b): β -diversity analyses performed on all mucosal samples by UniFrac algorithms showed a separation among the 3 groups, and PCoA revealed microbial structural differences [22].

ing 2019 that the difference in the prevalence of IgE-mediated serological food hypersensitivity was not observed between IBS-D and healthy controls. However, the cytokine profile was different depending on the presence of serological food hypersensitivity, and the patients with food hypersensitivity showed lower serum inflammatory cytokine levels than those without [17]. A serological test for food hypersensitivity would be the option to detect a specific cluster among patients with IBS-D.

Gut Microbiome in IBS

Human commensal bacteria play a variety of important roles such as nutrient absorption, fermentation of dietary fiber, metabolism, and development of immune system and so on. Dysbiosis, abnormalities or changes in the composition of the commensal bacteria communities are known to be associated with the pathogenesis of various diseases including IBS as well as regulation of the gut-brain interaction. Intestinal commensal bacteria were divided into the 2 compartments, the luminal compartment and the mucosa-adherent compartment, which is known as mucosa-associated microbiota (MAM). Most studies have focused on the fecal microbiota, which are predom-

inantly resident in the lumen, while there is increasing attention about more stable MAM. Recent studies indicated the difference in the bacterial community profile of MAM using brush samples during endoscopic procedures from that of fecal sample. The differences between feces and MAM became more notable at the family and genus levels [18–21]. However, most previous studies investigating the intestinal microbiota of IBS had used fecal samples, and only a few studies almost using biopsy samples had investigated MAM. Moreover, there are few articles evaluating MAM using brushing samples and the comparison among the IBS subtypes.

In the annual meeting 2020, Matsumoto et al. [22] indicated that the difference in the MAM between IBS-D and IBS-C using brushing samples taken from the ileum end and sigmoid of IBS patients and controls. The α -diversity and β -diversity indices were significantly different among the 3 groups (Fig. 3) like as previous studies [23]. *Roseburia* and *Butyricicoccus* were less abundant in the IBS groups, especially in the IBS-C, and the decrease may be consequences of butyrate reduction affecting colonic motility, immunity maintenance, and anti-inflammatory properties [24]. Genus *Dorea* was the most significantly different among the 3 groups and was more abundant in the IBS-C, which is consistent with previous

studies using stool samples [18]. The abundance of genus *Dorea* is associated with increased gas production and intestinal permeability, which is thought to contribute to the IBS pathophysiology. Dysbiosis pattern and the function of the microbiome seem to be different among subtypes of IBS, and MAM may play a crucial role in IBS symptom generation.

Psychosocial Factors

Psychosocial factors are affecting some behaviors and gut environments are interacting to psychosocial factors, and vice versa. In animal autism spectrum disorders model, an offspring born from hyperimmunized mother, altered gut microbiome (dysbiosis) might be contributed to the outcome of unique behavior like autism, and fecal microbiota transplantation has improved the altered behaviors [25]. Therefore, the investigations on the pathophysiological linkage between gut environmental factors and psychosocial factors are needed to understand such disorders. The scientific backgrounds are very similar to the pathophysiology of FGIDs in terms of gut-brain interaction. IBS patients often experienced physical abuse as children, and the infantile stress following additional acute stress in adulthood is thought to cause colonic hypermotility, barrier dysfunction (mucosal permeability), and visceral hypersensitivity via various neurotransmitters [26].

Maternal separation is a well-established experimental animal model of early life stress. In a previous study using maternally separated rats with acute stress (IBS rat model), the early life stress induced colonic hypercontraction. This physiological abnormality was partially induced by EGCs infiltrated in the colon [27]. EGCs might play important roles in mucosal barrier function, enteric neurotransmission, neuronal protection, and neurogenesis [28].

In another study, maternally separated IBS rat models are confirmed to indicate increased intestinal permeability and hypersensitivity to stress as well as an imbalanced gut microbiota, and interestingly, the hypersensitivity seems to be prevented by probiotic BBG9-1 administration in the animal model [29]. Further, the same group investigated the association between FD and the early life stress, and they evaluated visceral hypersensitivity by examining electrical activity of mitral muscles using electromyography under gastric distention. The results were reported by Kondo et al. in the annual meeting 2020 that gastric hypersensitivity and delayed emptying both were observed in maternally separated rats.

Conclusion

Recent research has shown major advances in understanding the pathophysiology of FGIDs. In this meeting review, highly impacted articles presented at JGA core symposium were introduced. FGIDs are much complicated because many factors in gut as well as in CNS/brain are interacted in bi-directions. This review was summarized according to this bidirectional concept, which are including visceral hypersensitivity and sensor, inflammation and immune dysfunction, microbiota in gut and psychosocial factors with early life stress (maternally separated rat model) in CNS/brain, and these interactions. For better understanding of these interactions, the researches on the molecular basis of each associated factors are required. At present, it is ongoing, and we are just touching to the clue for understanding of these complicated interactions. More comprehensive research works, including GI physiology and psychosocial factors will be eagerly desired.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

T.S. has contributed to plan the manuscript structure for the JGA meeting reports and manuscript writing. A.S. has contributed to manuscript writing. Both have approved the final manuscript.

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