Words of Editor-in-Chief

Psychosomatic Gastroenterology (PG) is the official academic journal of Chinese Digestive Psychosomatic Union (CDPU), which was founded in April 2016 in Shanghai, China. It is the first global journal focusing on "psychosomatic gastroenterology".

Psychosomatic Gastroenterology is an open access, peer-reviewed journal that covers basic and clinical research, therapeutics and education for all aspects of psychosomatic gastroenterology, including the mechanism research and therapeutic research. The accepted articles include original research, reviews, case reports, expert experience, academic event reports and so on. *Psychosomatic Gastroenterology* creates a novel interface between the fields of social, psychological and biological research.

We hope *Psychosomatic Gastroenterology* would play an important role in promoting the management of gastrointestinal diseases in which psychological mechanisms may be involved. And, we look forward to publishing more and more your papers with great importance in psychosomatic gastroenterology.

Chairman of Chinese Digestive Psychosomatic Union
Chief of Chinese Association of Psychosomatic Digestive Diseases
Professor of Department of Gastroenterology

Table of Contents

Volume 2, Number 2, December 2019

Psychosom Gastroenterol 2019; 2(2): 65-70

Brain-gut interactions and management of gastrointestinal motility disorders

Li Cheng, Sheng-Liang Chen
Division of Gastroenterology and Hepatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, Institute of Digestive Disease, Shanghai, China

Abstract: Gastrointestinal dysmotility is involved in the pathogenesis of almost all of the disorders of gastrointestinal tract. This article addresses the relationships between dysmotility of various parts of the gastrointestinal tract with the holistic medical philosophy of psychosomatic gastroenterology. The research progresses about psychosomatic medicine, neurogastroenterology, intestinal microbiota and brain-gut interactions were discussed. This article provides medication strategies for refractory gastrointestinal disorders in clinical practice.
Key words: gastrointestinal motility; psychosomatic gastroenterology;brain-gut axis.

Introduction

Gastrointestinal (GI) dysmotility is the first recognized important pathogenesis of functional GI disorders (FGIDs)[1-2]. Nevertheless, now it is still a major challenge to treating GI motility disorders, especially those comorbid with psychological disorders. The reasons for this phenomenon include: (i) the unknown etiology and pathogenesis of motility dysfunction due to the complex motion state in various parts of the GI tract, (ii) the lack of definite relationships between motility dysfunction and symptoms, and (iii) the limited choices of available medications capable of regulating GI motility [1,3].

In recent years, the basic researches on intestinal microbiota and brain-gut interactions as well as the clinical experience of psychosomatic gastroenterology have made great progresses. The application of drugs capable of alleviating GI inflammatory responses, regulating microbiota, or regulating neurotransmitters has improved the management of FGIDs[1]. However, relevant basic knowledge and clinical experience remain to be accumulated and summarized. In this review, we discussed about (i) the innervation of GI tract and the motion state of various parts in GI tract under physiological conditions, (ii) the effect of psychosocial and intraluminal factors on the characteristics of GI motility dysfunctions, (iii) the clinical implications of GI dysmotility, and (iv) the treatment strategies with the concept of psychosomatic gastroenterology.

Esophagus

The muscles that dominate esophageal movement are divided into two parts. The upper 1/3 to 1/2 part is composed of striated muscles (skeletal muscles), and the lower 1/2 to 2/3 part is composed of smooth muscles, which contain the lower esophageal sphincter (LES) in the gastroesophageal junction area. The movement of the upper striated muscles is spontaneous swallowing movement dominated by consciousness. The lower smooth muscles are innervated by the autonomic nervous system. In addition to directly activated by acetylcholine, they are also regulated by nitric oxide, vasoactive intestinal peptide (VIP) and other neurotransmitters released by the enteric nervous system[4]. The sympathetic nerves play a dominant role in the contraction of smooth muscles of the esophagus body, whereas the parasympathetic nerves exert a major effect on the contraction of LES.

The functional changes of cerebral cortex that

Received 14 October, accepted 7 Decemder.
Correspondence to:Shengliang Chen,Email:chenslmd@163.com

dominate mental and psychological emotions can affect the motion state of esophageal smooth muscles through modulating functions of the autonomic nerves (via affecting the functional balance of sympathetic and parasympathetic nerves). Generally, the "irritant" emotional reactions, such as irritability and anxiety, tend to facilitate sympathetic functions and increase the invalid contraction of esophageal body, affecting swallowing fluency and clearance of the contents in esophageal lumen. In addition, mental stress often leads to the increase of invalid swallowing. The "irritant" emotional reactions also suppress the excitability of parasympathetic nerves and thus cause LES relaxation. Conversely, the "inhibitory" emotions, such as listlessness and depression, tend to decrease sympathetic tones and inhibit contraction of smooth muscles in the esophageal body. These emotions also increase parasympathetic activity, resulting in achalasia of LES. It is crucial for better understanding the mechanisms of esophageal dysmotility to clarify the influence of psychological and emotional factors on the motion state of esophagus.

According to the Chicago Classification criteria[5], esophageal motility disorders are divided into two types: (i) disorders with achalasia, which can be further divided into different subtypes according to the different motion states of smooth muscles in esophageal body. Medications such as 5-HT4 receptor agonists and antidepressants capable of promoting psychodynamic and sympathetic tones could be clinically effective. (ii) disorders without achalasia, which involve increased invalid peristalsis of smooth muscles in esophageal body. Medications such as dopamine D2 antagonists, sedatives and anti-anxiety agents, and nitric oxide precursors. The treatment strategies to ameliorate mucosal inflammation are also recommended.

Stomach

The factors affecting the physiological functions and pathological states of the stomach consist of the receptive relaxation of the gastric fundus, the resting tension of the gastric body, and the grinding and propulsion of the gastric antrum[6]. The activation of the sympathetic nerves can increase the peristalsis and tension of the circular muscles, an effect followed by the enhancement of longitudinal muscle contraction. Parasympathetic excitability is associated with the resting tension and achalasia of the sphincters. The smooth muscle layer in the gastric fundus are relatively thin. The main movement form of these muscles is receptive relaxation, which is controlled by the sympathetic tones. The smooth muscle layer in the corpus, which is divided into two layers, is relatively thick. The inner layer consists of circular muscles arrayed vertically and obliquely with the longitudinal axis of the stomach. The outer layer is composed of longitudinal muscles in line with the longitudinal axis. The smooth muscles in the antrum is most abundant. The circular muscles and longitudinal muscles move in coordination to promote chyme grinding in the antrum and propulsion of chyme toward the pylorus.

Mental and emotional status modulates the motion state of various parts of the stomach through affecting the balance between the sympathetic and parasympathetic tones, and thus are associated with various dysmotility symptoms and gastric mucosal damage[7]. Firstly, the "irritant" emotional status could impair postprandial receptive relaxation of the fundus, leading to symptoms such as early satiety and postprandial fullness. Activation of the sympathetic nerves can enhance the tension of smooth muscles in the body, restricting the flow of chyme in the fundus to the body after meals and thus increase the friction between mucous membrane and chyme. These effects could aggravate postprandial distension symptoms and cause inflammation and damage in plicae and mucosa of the body. Moreover, the "irritant" emotions could promote the contraction and peristalsis of circular muscles in the antrum, leading to narrowing of the space in the coronal plane of the antrum. This may increase the risk of mucosal damage due to excessive abrading by chyme. Secondly, the "inhibitory" emotions such as listlessness and depression may lead to down-regulation of the autonomic tones and subsequent decrease of gastric smooth muscle contraction and peristalsis. This may impair the postprandial flow-limiting effect of gastric body, resulting in abnormal distribution of chyme in the stomach (e.g., too fast and excessive flow toward the antrum) and postprandial distension symptoms. Meanwhile, chyme grinding in the antrum and

propulsion of chyme toward the pylorus could increase. Under this condition, antral mucosal damage caused by physical and chemical components of gastric contents may be aggravated.

According to the psychosomatic factors and clinical manifestations, gastric motility disorders can be classified into three types: (i) receptive dysfunction of the fundus accompanied with increased contraction of circular muscles in the body. Clinical manifestations include early satiety and postprandial distention, fundus mucosal injury, and longitudinal mucosal injury in the body (or antrum). Prokinetic agents such as dopamine D2 antagonists are recommended. For refractory cases, psychoactive agents, such as small dose of tricyclic antidepressants (TCAs), 5-HT1A agonists, and selective serotonin reuptake inhibitors (SSRIs), can be applied. (ii) contraction dysfunction of the body, which leads to too fast flow of chyme toward the antrum after meals. Clinical manifestations include postprandial distension and poor appetites. Recommended medications include 5-HT4 agonists and dopamine D2 antagonists. In refractory cases, antidepressants such as SSRIs (fluoxetine, sertraline, and citalopram, etc.) can be used to enhance mental motivation and autonomic excitability. (iii) contraction dysfunction of the antrum. Clinical manifestations include upper abdominal discomfort, postprandial distension, and diffused mucosal damage. The recommended medications include dopamine D2 antagonists, 5-HT4 agonists, antidepressants, etc.

Duodenum and sphincter of Oddi

The role of dysfunction of the duodenum and sphincter of Oddi in the pathogenesis of FGIDs (and organic GI diseases) has been severely underestimated in the current clinical treatment guidelines. Actually, the functional state of the duodenum and sphincter of Oddi dominates the digestion and absorption efficiency of the small intestines and influences the environment of the distal part of the small intestines. Therefore, it is critical in regulation of the intestinal microflora-mucosal inflammation and the gut-liver-brain pathway. In addition, dysfunction of the duodenum and sphincter of Oddi may cause poor emptying of biliopancreatic duct or enteric-biliopancreatic duct reflux, which leads to biliopancreatic diseases. Duodenal motion state also directly or indirectly affects gastric emptying and is associated with the pathogenesis of enterogastric-esophageal reflux.

Duodenal movement under physiological conditions can be divided into two forms [8]: (i) the postprandial segmentation movement dominated by circular muscles, which is characterized by subtle annular constrictions without obvious shortening in the longitudinal axis. The duodenal smooth muscles interweaving with sphincter of Oddi play a "doorknob" role to promote sphincter of Oddi opening and subsequent release of bile acids and digestive proenzymes into the duodenal lumen. The segmentation movement of the duodenum is essential for adequate mixing of chyme with bile acids and digestive enzymes and subsequent digestion of chyme. (ii) The migrating motor complex (MMC)in fasting state dominated by longitudinal muscles, which is accompanied by shortening in the longitudinal axis of the duodenum and closing of sphincter of Oddi. This type of movement promotes the rapid emptying of chyme in the proximal part of the small intestines and reduces exposure of the intestinal mucosa to bile acids, digestive enzymes, microorganisms and other injury factors.

The coordinated movement of the duodenum and sphincter of Oddi depends on the complex interactions of neuroendocrine and paracrine mechanisms. Psychological and emotional status may affect the movement of the duodenum and sphincter of Oddi. The underlying mechanisms involve neuroendocrine, immuno-inflammatory responses, and changes in diet-related behaviors[9-11]. Under pathological conditions such as local mucosal inflammation, the increased sympathetic excitability caused by the "irritant" emotional responses may lead to disturbed food-intake rhythm. The postprandial movement phase of the duodenum, as well as the opening of sphincter of Oddi, could thus be prolonged, resulting in increased exposure of bile acids and digestive enzymes and reflux of intestinal contents into the biliopancreatic duct. This abnormal motion state could be associated with a variety of GI disorders, including: (i) gastroesophageal reflux disease and bile reflux gastritis, (ii) small intestinal bacterial overgrowth (SIBO) caused by poor emptying of the proximal part

of the small intestines, and (iii) the decreased digestion and absorption efficiency in the proximal part and the deteriorated physical, chemical and microecological environment in the distal part of the small intestines, which result in inflammatory bowel disease, liver diseases, and systemic diseases associated with dysregulation of the gut-brain axis. On the other hand, the negative psychological emotions are often accompanied by decreased autonomic tone, resulting in dysfunction of duodenal movement (especially MMC) and sphincter of Oddi. The clinical manifestations include duodenal stasis, periodic vomiting, duodenal renal artery compression, biliary sludge, and recurrent pancreatitis[10].

According to the principles of psychosomatic gastroenterology, the recommended medications for the three types of dysmotility of the duodenum and sphincter of Oddi are as following: (i) type I (characterized by prolonged postprandial movement phase and excessive opening of sphincter of Oddi). The recommended medications include local calcium channel antagonists, cholinergic receptors antagonists, dopamine D2 antagonists, anti-anxiety agents, antidepressants like TCAs, and drugs capable of ameliorating duodenal mucosal inflammation; (ii) type II (characterized by excessive fasting MMC). Treatment strategies include alleviating mucosal inflammation and improving intestinal environment; (iii) Type III (characterized by decreased duodenal movement). 5-HT4 receptor agonists, antidepressants such as SSRIs, serotonin and norepinephrine reuptake inhibitors (SNRIs), etc., and choleretic drugs can be applied.

Colon and anal canal

The movement pattern of the colon is similar to that of the small intestines, consisting of the circular muscle-dominated segmental movement and the longitudinal muscle-dominated MMC. The abnormal motion state of the entire colon and defecation movement of the anal canal-anal sphincter are often associated with the lower GI disorders via affecting gastrocolic reflex[12-13]. The gastrocolic reflex is a physiological reflex controlling the motility of the lower GI tract following a meal. Upon the gastrocolic reflex, the colon has enhanced motility in response to the stretch of the stomach with the ingestion of food[14]. Normal gastrocolic reflex is essential in the transmission of feces in the colonic lumen and the formation of defecation awareness[15-16], while exaggerated gastrocolic reflex may cause postprandial abdominal distension (usually occurs 1 - 2 hours after a meal) and even uncontrolled defecation after meals. Dysfunction of colonic smooth muscles as well as certain molecules (such as nitric oxide) produced under the pathological conditions of the intestines may impair colonic motility, leading to constipation, paralytic ileus, and even toxic megacolon. The luminal physical, chemical stimulants and mucosal inflammation often enhance colonic motility and induce borborygmus and diarrhea. Positive psychological reactions, such as irritability and anxiety, often lead to enhanced colonic movement and transmission. On the other hand, negative psychological responses such as listlessness and depression are often accompanied by reduced colon movement and clinical manifestations including dry stool, hard stool, reduced frequency of defecation and lack of defecation awareness. Fecal characteristics correspond well with colonic motion state[17]. Colonic motility disorders can be classified into three types according to stool shapes: (i) type I (with mushy stools). Recommended treatments include calcium channel antagonists, cholinergic receptor antagonists, anti-anxiety agents, anti-inflammatory agents, probiotics, and short-term application of acid-secretion inhibitors (to reduce gastrocolic response sensitivity); (ii) type II (with hard stools). 5-HT4 receptor agonists, antidepressants, secretory stimulants, osmotic laxatives, and metabolism-regulating probiotics can be applied. (iii) Type III (with alternating stool shapes). Therapeutic medications include drugs regulating intestinal motility, anti-inflammatory agents, antidepressants, anxiolytics and biofeedback therapies.

The etiology and pathogenesis of anal canal-anus dysmotility are complicated. They involve not only the colonic dysmotility, but also the psychological factors[18-20]. Further details are not described in this article. Clinical complaints related to defecation including altered defecation frequency, dry and hard stools or other abnormal stool forms, defecation urge deficiency, exertion in defecation, poor stool output and anal distension and pain, etc. Based on the characteristics of feces, the functional

abnormalities of anal canal-anus defecation and corresponding treatments are briefly summarized as follows: (i) type I disorder (separate lumps or strips-like stools). Therapeutic treatments include mucosa-stimulating laxatives, osmotic laxatives, 5-HT4 receptor agonists, secretory stimulants, biofeedback therapies, antidepressants and anxiolytics, low-dose antipsychotics, cognition improvement, and short-term application of proton pump inhibitors to decrease gastro-colonic sensitivity (still lack of evidence-based basis); (ii) type II disorder (with mushy stool). Recommendations are anti-inflammatory agents, anxiolytics, low-dose antipsychotics, and biofeedback therapeutics, etc.

In conclusion, GI dysmotility contributes to the pathogenesis of GI disorders. It is closely associated with dysregulation of brain-gut axis. In this article, the etiology of GI dysmotility, clinical associations and treatment strategies are discussed from the perspective of psychosomatic gastroenterology.

References

1. Keefer L, Palsson OS, Pandolfino JE. Best practice update: incorporating psychosomatic gastroenterology into management of digestive disorders. Gastroenterology. 2018;154:1249-1257.
2. Törnblom H, Simrén M, Abrahamsson H. Gastrointestinal motility and neurogastroenterology. Scand J Gastroenterol. 2015;50:685-697.
3. Yu Tien Wang, Kah Foo Victor Kwok, Shian Ming Tan, et al. Comprehensive psychological intervention to improve outcome in functional gastrointestinal disorder: a cohort study. Singapore Med J. 2015; 56: 385-392.
4. Tae Hoon Kwon, Hyunwoo Jung, Eun Jeong Cho, et al. The Signaling mechanism of contraction induced by ATP and UTP in feline esophageal smooth muscle cells. Mol Cells. 2015; 38: 616-623.
5. International High Resolution Manometry Working Group. The Chicago classification of esophageal motility disorders, V3.0. Neurogastroenterol Motil. 2015; 27: 160-174.
6. Burks TF, Galligan JJ, Porreca F, et al. Regulation of gastric emptying.Fed Proc. 1985;44:2897-2901.
7. Kirsteen N, Browning R, Alberto Travagli. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. Compr Physiol. 2014; 4: 1339-1368.
8. Worthley CS, Baker RA, Iannos J, et al. Human fasting and postprandial sphincter of Oddi motility. Br J Surg. 1989;76:709-714.
9. Muller EL, Grace PA, Conter RL, et al. Influence of motilin and cholecystokinin on sphincter of Oddi and duodenal mobility. Am J Physiol. 1987;253:G679-683.
10. Coelho JC, Wiederkehr JC. Motility of Oddi's sphincter: recent developments and clinical applications. Am J Surg. 1996;172:48-51.
11. Yoo BM, Kim JH, Yang MJ, et al. Cyclic change of sphincter of Oddi motility and its relationship with small bowel migrating motor complex in humans. Dig Dis Sci. 2018;63:3425-3433.
12. Sims MA, Hasler WL, Chey WD, et al. Hyperglycemia inhibits mechanoreceptor-mediated gastrocolonic responses and colonic peristaltic reflexes in healthy humans. Gastroenterology. 1995;108:350-359.
13. Björnsson ES, Chey WD, Ladabaum U, et alDifferential 5-HT3 mediation of human gastrocolonic response and colonic peristaltic reflex. Am J Physiol. 1998;275:G498-505.
14. Malone JC, Thavamani A. Physiology, gastrocolic reflex (gastrocolic response). StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 .
15. Björnsson ES, Chey WD, Hooper F, et al. Impaired gastrocolonic response and peristaltic reflex in slow-transit constipation: role of 5-HT3 pathways. Am J Physiol Gastrointest Liver Physiol. 2002;283:G400-407.
16. Führer M, Hammer J. Lack of an effect of gastric capsaicin on the rectal component of the gastrocolonic response. Dig Dis Sci. 2017;62:3542-3549.
17. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterol. 1997;32:920-924.
18. Patcharatrakul T, Rao SSC. Update on the pathophysiology and management of anorectal disorders. Gut Liver. 2018;12:375-384.
19. Simón MA, Bueno AM. Relevance of the clinical and psychophysiological variables in the dyssynergic defecation: a comparative study in

elderly subjects. Appl Psychophysiol Biofeedback. 2017;42:203-208.
20. Sharma A, Rao S. Constipation: pathophysiology and current therapeutic approaches. Handb Exp Pharmacol. 2017;239:59-74.