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

VOL3, NO2 Dec 2020

Application of neurotransmitter regulators in refractory functional gastrointestinal disorders

Cheng Li, Bo Wang, Sheng- liang Chen.
Department of Gastroenterology, Renji hospital, Shanghai Jiaotong university school of medicine, Shanghai institute of digestive diseases, Shanghai 200001, China

Abstract: The application of neurotransmitter regulators (mainly antidepressants) is one of the theoretical and practical breakthroughs to improve the therapeutic efficacy of refractory functional gastrointestinal disorders (rFGIDs). The targets of neurotransmitter regulators in FGIDs treatment include: (i) psychological factors as etiology; (ii) clinical manifestations of psychological complications associated with FGIDs; (iii) the mechanisms of central and peripheral nervous dysregulation on gastrointestinal functions (movement, secretion and sensation, etc.). Based on the thinking of "gut-brain interaction"and basic mechanisms of neurogastroenterology, this article discusses about the practical strategy in digestive specialty for neurotransmitter regulators (mainly antidepressants) in the treatment of psychological factors-related rFGIDs in many aspects. The items include selecting drug varieties, dosage, course of treatment, compliance, efficacy, and safety.

Key words: functional gastrointestinal disorders;gut-brain interaction; digestive psychosomatic gastroenterology; gastrointestinal motility; visceral hypersensitivity

Recieved 10 October, accepted 15 November

Introduction

Functional gastrointestinal disorders (FGIDs) are a series of disorders with gastrointestinal symptoms but cannot be found any explainable etiology within the scope of routine examinations (including laboratory tests and endoscopy). At present, the proportion of FGIDs in digestive specialty clinics is over 50%. With the change of society, human living environment and living behaviors, the prevalence and consultation rate of FGIDs are showing an increasing trend[1,2]. Refractory functional gastrointestinal disorders (rFGIDs) generally refer to patients who follow the standard treatment of digestive symptoms and undertake conventional medication treatment for over 12 weeks, but are unable to reach a satisfying curative effect (the improvement rate of symptoms is less than 50%). Clinical features of rFGIDs include: (i) drug resistance of routine digestive specialty medications; (ii) combination of psychological factors; (iii) overlaps in complex symptoms. The proper use of neurotransmitter regulators such as antidepressants is one of breakthroughs in improving the therapeutic efficacy of rFGIDs[2].

However, the international literature and consensus on the antidepressant therapy strategies in FGIDs treatment are limited, and the only documents available to guide the application are formulated from the perspective of psychiatry and psychology[1]. Actually, the pathophysiological and clinical changes of FGIDs in gastrointestinal tract are the result of comprehensive effect of "gut-brain interaction". Therefore, it is difficult to obtain an ideal and curative guideline for the use of neurotransmitter regulators in FGIDs from a purely psychological perspective. In recent years, with the implementation of Mental Health Law, medical system reform and Healthy China strategy, Chinese specialists and scholars have attained abundant knowledge about basic research and clinical practice in digestive specialty (especially rFGIDs-related). In addition, more details about the application of neurotransmitter regulators in rFGIDs have been further explored. "The expert opinions on the treatment of digestive psychosomatic health problems in China" published in 2016 have demonstrated more specific guidance, marking that the research on the application of neurotransmitter regulators in the treatment of digestive psychosomatic health problems in China is taking the lead worldwide.

The direct goal of neurotransmitter regulators in the treatment of rFGIDs is to eliminate or relieve digestive symptoms, rather than the psychological problems unsupported explicitly by laws and regulations. Digestive specialty characteristics should be integrated throughout the selection of drug varieties (targeting on pathophysiological mechanisms), dosage, course of treatment, withdrawal, patient compliance, safety, as well as laws and regulations. More details will be delineated below and are hoped to provide some reference.

Management of gastrointestinal motility disorders

The primary mechanism underlying the influence of emotional fluctuations on the motion state of various gastrointestinal segments, is to trigger the functional imbalance of autonomic nerves (sympathetic and/or parasympathetic nerves). This ultimately shifts to the intrinsic enteric nerve system and affects the resting tension and motion state of smooth muscle (circular muscle, longitudinal muscle and sphincter) throughout the digestive tract[3,4] .Generally, the smooth muscle of esophagus body and circular muscle in digestive tract are dominated by the output effect of sympathetic nerve, while the upper and lower esophageal sphincter (UES and LES), pyloric sphincter and Oddi sphincter are prone to parasympathetic effect. Meanwhile, the overall function of autonomic nerves is reduced and subsequently caused the poor coordination of gastrointestinal smooth muscle movement.

The association between emotional phenotypes and clinical manifestations of FGIDs can be summarized into two polarized presentations: (i) the irritant or anxious emotional reactions correspond to a series of movement disorders, such as increased invalid contractions of esophageal body, decreased ability to clear contents in the esophageal lumen, reduced resting tension of LES, and even distal spasms (the Nutcraker esophagus). In addition, the receptive relaxation function of gastric fundus declines, and the tension of circular muscle in stomach body and antrum increases, resulting in a feeling of obvious postprandial discomfort. In duodenum, the increased circular muscle

tension and peristalsis, along with the excessive open state of Oddi sphincter, lead to constant and increased exposure to bile acid in the intestinal cavity. Therefore, the probability of gastric bile reflux, duodenal content reflux to bile duct (and pancreatic duct), and biliary tract inflammation increases. With the increased peristalsis of colonic annular muscle and longitudinal muscle, some clinical symptoms such as barborygmus and diarrhea gradually appear. On the contrary, (ii) the inhibitory or depressed emotional reactions cause declined peristalsis and weakened smooth muscle tension in esophageal body, as well as unrelaxed LES, which may be related to cardia achalasia. The deficient peristalsis and decreased resting tension of gastric smooth muscle result in abnormal distribution of chyme in stomach after meals. In addition, similar muscle dysfunction in duodenum may be related to duodenal stasis, poor open function of Oddi sphincter, and bile duct (and pancreatic duct) stasis, while in colon it hinders the intestinal content transmission and causes constipation.

The gastrointestinal dysmotility is one of major targets in the application of neurotransmitter regulators in FGIDs[5-8]. Dysmotility associated with irritant emotions is often treated with sedative and anti-anxiety neurotransmitter drugs. Antidepressants with anti-anxiety effect can be applied, such as selective 5- HT reuptake inhibitors (SSRIs) like fluvoxamine, paroxetine, citalopram (or escitalopram), 5-HT receptor antagonist and/or reuptake inhibitor (SARI) trazodone, and benzodiazepine sedatives, etc. For dysmotility related to depressed emotions, antidepressants such as SSRIs fluoxetine, sertraline are recommended. Considering that the main treatment goal of digestive specialty focuses on gastrointestinal dysmotility rather than psychological problems, these medications should be used in small doses and short course of treatment. Besides, peripheral effect should be emphasized when communicating with patients, which can help improve patient compliance and reduce adverse reactions at the early stage of treatment[1,2,5]. Long-term observation and studies are still needed to conclude more specific characteristics of curative effect and the regularity of dose and course.

At present, the mechanism of some conventional prokinetic agents and their effect on the motor characteristics of gastrointestinal tract have been confirmed relatively[9,10]. Dopamine D2 receptor antagonist can increase the tension of LES, strengthen the contraction of gastric antrum and promote the opening of pylorus. It also helps alleviate gastroesophageal reflux and promote gastric emptying. Currently, major prokinetic agents on market in China include metoclopramide, domeperidone, itopride and cinitapride. Another type of prokinetic agents is 5-HT3 receptor agonist, which helps promote the movement of smooth muscle in esophagus body and whole gastrointestinal tract, and improve the scavenging function of esophagus. Medications include mosapride , prukalopride, cinitapride, etc. Previously, cisapride and tegaserod were also applied but have been delisted in view of their cardiovascular safety problems. In cases of rFGIDs that cannot achieve satisfactory efficacy with conventional gastrointestinal motility agents, neurotransmitter regulators can be alternatively applied. The two medications overlap in pharmacology, so a combined use is not recommended.

Management of visceral hypersensitivity

As another core pathogenesis of FGIDs, gastrointestinal visceral hypersensitivity (VH) refers to the sensitive response of gastrointestinal tract to subliminal, non-invasive stimuli[11,12]. The etiology and pathogenesis involve functional changes of both central and peripheral nervous system[13]. In central nervous system, psychological stress and other factors induce functional changes of cerebral cortex, which may disturb or inhibit the working state of the midbrain nuclei related to analgesia. Once the excitability of these nuclei are hindered, the inhibiting effect on the descending pathway of pain response in spinal cord is reduced[14]. In peripheral nervous system, two nerve pathways in vagus and spinal cord mediate the chronic pain perceptions and responses. Stimulating factors (neurotransmitters, chemical substances, metabolites, peptide hormones, inflammatory factors) in the inflammatory environment (including gastrointestinal tract) stimulate sensory nerve endings, facilitate the afferent and efferent signaling of spinal dorsal horn sensory nerve fibers, and amplify the sensation of stimulus. The stimulating factors in gastrointestinal

tract gradually impair the inhibiting effect of vagus afferent nerve on nociception pathway[15-19]. Neurotransmitter regulators target the pain regulatory mechanisms of central and peripheral nerves and contribute to the amelioration of VH symptoms in FGIDs. In central, drugs increase the concentration of neurotransmitters in synaptic gaps, and rebalance the receptor expression on presynaptic and postsynaptic membranes in feedback, restoring the homeostasis of pain regulation under physiological state. In peripheral, neurotransmitters reduce VH through a direct effect on nerves or indirectly modulating the inflammatory microenvironment and organ functions. Therefore, according to different pathogenesis of individuals, the effect of the central and peripheral nervous system should be considered carefully when selecting the appropriate drug types, dosage and course of treatment. For improvement in central nervous system, treatment regimen is recommended in accordance with psychiatric specialty, while a reasonably small dose and short course of treatment should be applied in purpose of peripheral regulation.

Management of intestinal inflammation

The persistent low-grade mucosal inflammation of gastrointestinal mucosa participates in the pathophysiology of gastrointestinal dysmotility and VH. The "brain-gut interaction" is also an important regulatory mechanism of anti-infection and anti-inflammation responses in gastrointestinal mucosa[20-22]. First of all, stress and psychological reactions induce the functional changes in insular cortex, which subsequently cause gastrointestinal mucosal inflammation through regulating the hypothalamic-pituitary-adrenal (HPA) axis and the cholinergic anti-inflammatory effect of the autonomic nerve (vagus efferent nerve). An increasing number of animal experiments and clinical studies have confirmed that appropriate antidepressants (TCAs, SSRI, SNRI, etc.) can ameliorate mucosal inflammation in inflammatory bowel disease (IBD)[23]. Aside from central function, the three neurotransmitters involved in antidepressants (dopamine, 5-HT, and norepinephrine) all play a complex regulatory role in the inflammatory response. Herein, antidepressants may contribute to the FGIDs treatment due to their anti-inflammatory effect.

Digestive specialty characteristics in application of neurotransmitter regulators

In general, the involvement of psychological factors in the specific pathophysiological mechanisms of the occurrence and development of digestive diseases is highly individualized. Unlike the clinical practice in psychiatric specialty, the problems gastroenterologists encountered are digestive symptoms and diseases rather than mental disorders. Therefore, in the application of neurotransmitter regulators for digestive diseases, the drug varieties, dosage and treatment courses vary from those for psychiatric diseases. Different theoretical and practical characteristics should be considered for a better combination of the central and peripheral nervous, neuroendocrine and immune regulatory effects. In particular, the management of gastrointestinal pathophysiology should follow the guidance of theoretical basis and clinical practice of digestive psychosomatic holistic medicine. A comprehensive thinking and interdisciplinary methods among psychiatry, psychology, behavioral science and neuroendocrine immunity, are beneficial for further researches on digestive pathophysiology and mastering the functional characteristics of neurotransmitter regulators including the central and peripheral nervous, immune, endocrine effect, and especially the direct effect on digestive organs and tissues. The current and future striving direction is to establish a theoretical and practical guideline for digestive specialized application of neurotransmitter regulators in psychosomatic digestive diseases. For digestive specialists, three key points are suggested: (i) To establish a holistic thinking of psychosomatic digestion. The concept of psychosomatic holistic medicine helps specialists identify the psychological or emotional abnormalities, as well as the pathophysiology of the digestive system when dealing with digestive clinical problems. (ii) To master the detailed pharmacological characteristics of commonly used neurotransmitter regulators. (iii) To figure out a practical strategy for neurotransmitter drugs application in digestive specialty, including the selection of appropriate medications, the determination of dose and treatment course according to different

target and effect.

In central nervous system, three types of neurotransmitters are mainly adjusted by neurotransmitter regulators, namely serotonin, norepinephrine and dopamine. They jointly affect a series of mental activities like mood, emotion, impulse, desire, energy, interest, will, desire and motivation, etc. In peripheral, they also involve the regulation of visceral function and blood circulation. Thus, transmitters affect the somatic and visceral sensitivity through acting on both central and peripehral nervous system. In addition, these neurotransmitters contribute to regulation of physiological and pathological conditions during systemic inflammatory responses through participating in neuroendocrine and immune regulatory networks. They also exert a direct or indirect regulatory effect on the gastrointestinal tract movement, secretion and sensation.

Neurotransmitter regulators exert their therapeutic effect on the functional abnormalities of central nervous system through inhibiting the neurotransmitter re-uptake and increasing the concentrations of neurotransmitters (serotonin and norepinephrine, etc.) in synaptic clefts, which trigger the postsynaptic membrane receptors to readjust the abundance and functions. These receptor proteins first go through the synthesis-assembly process (including DNA replication in nuclei-DNA transcription–RNA translation–protein modification–transportation onto synaptic membranes–proper assembly) in neurons, which means that the antidepressants take curative effect on central nerves at least 2~6 weeks later, and an efficacy plateau can be reached in 8~10 weeks. On the contrary, in peripheral, neurotransmitters primarily take direct effect on the gastrointestinal target tissues (e.g., smooth muscle, glands). Accordingly, the therapeutic effect on gastrointestinal tract takes effect quickly, mostly in a few days to 2 weeks, and the efficacy plateau can be reached in 4 weeks. There are a few guiding principles for the application of neurotransmitter regulators: (i) For cases primarily induced by psychological problems, the main therapeutic goal is to deal with psychological problems. Physicians should refer to the treatment guidelines for psychiatric specialty. Qualified psychiatric specialists should make a clear diagnosis and a detailed assessment, as well as the formulation of selection of drugs and treatment course. Meanwhile, digestive specialists should perform their obligations and consultations to assist and manage digestive problems. The selection of neurotransmitter drugs mainly aims at the indications of psychological problems, while the avoidance or reduction of gastrointestinal adverse reactions is also taken into account[24-25]. The course of treatment generally follows the guidelines and norms for psychiatric specialty and often shows a dose-dependent efficacy. A gradual withdrawal is recommended after the efficacy is consolidated (generally a full course for at least 6 months). (ii) Among patients visiting for digest symptoms, which are the main complaints and disposal objects, psychological or emotional disorders often accompany. Yet the severity has not reached diagnostic criteria for psychological diseases, so psychological problems cannot be recognized as the major clinical problems and the original etiology. The selection of drugs should consider the treatment mechanism of both psychophysiology and gastrointestinal pathophysiology. It is advisable to start with a small dose and increase gradually until reaching the satisfactory efficacy. The longer the onset time, the more sustaining process it needs for consolidation and gradual withdrawal. For patients with rapid onset and satisfactory efficacy, the treatment course management can refer to that of commonly used drugs in digestive specialty. (iii) For some patients that cannot achieve a satisfactory efficacy with standard medical treatment of digestive specialty, although there is no identifiable psychological problem, small doses of neurotransmitter regulators are recommended. The therapeutic mechanism of regulators is speculated to direct target the peripheral nerves and gastrointestinal organs and tissues. The treatment course management can refer to the application of commonly used drugs in digestive specialty.

Conclusion

The application of neurotransmitter regulators in improving the efficacy of rFGIDs is the future direction for developing the theory and practice of holistic psychosomatic medicine. With increasing clinical challenges, the initial intention is to solve clinical problems and benefit patients. The medical

decisions should be patient-centered, guarantee informed consent, and respect patients' choices and subjective willingness. It should be emphasized that, the application of neurotransmitter regulators must be within the framework of existing laws (Mental Health Law) and regulations, as well as the various rules and regulations at all levels of medical and health institutions. The majority of viewpoints in this article are based on related literature and clinical experience of some experts. At present, the level of evidence is insufficient for reaching a consensus or a guideline, and is only available for readers to achieve a better understanding. Criticism and opinions are welcomed regarding to the inaccurate or inadequate information in this article.

References

1. Drossman DA, Hasler WL. Rome IV- Functional GI Disorders: Disorders of Gut-Brain Interaction. Gastroenterology.2016;150 (6):1257-1261.
2. Chinese Society of Gastroenterology Gastrointestinal Kinetics Group. Gastrointestinal Functional diseases Collaboration Group. The expert opinions on the treatment of digestive psychosomatic health problems in China (in Chinese, 2015).Chin J Dig.2016;36(4): 217-229.
3. Drossman DA, Tack J, Ford AC, et al. Neuromodulators for Functional Gastrointestinal Disorders (Disorders of Gut- Brain Interaction): A Rome Foundation Working Team Report. Gastroenterology. 2018 ;154(4):1140-1171.
4. Bonaz B, Sinniger V, Pellissier S. Vagal tone: effects on sensitivity, motility, and inflammation. Neurogastroenterol Motil.2016;28(4): 455-462.
5. Sobin WH, Heinrich TW, Drossman DA. Central Neuromodulators for Treating Functional GI Disorders: A Primer. Am J Gastroenterol.2017;112(5):693-702.
6. Gershon MD, Tack J. The serotonin signaling system: from basic understanding to drug development for functional GI disorders. Gastroenterology.2007;132(1):397-414.
7. Israelyan N, Del Colle A, Li Z, et al. Effects of Serotonin and Slow- Release 5-Hydroxytryptophan on Gastrointestinal Motility in a Mouse Model of Depression. Gastroenterology.2019;157(2):507-521.
8. Kindt S, Tack J. Mechanisms of serotonergic agents for treatment of gastrointestinal motility and functional bowel disorders. Neurogastroenterol Motil. 2007;19 (Suppl 2):32-39.
9. Dolina J, Hep A, Kunovsky L, et al. Prokinetics and their use in gastroenterology. Vnitr Lek. 2018;64(6):673-678.
10. Quigley EMM. Prokinetics in the Management of Functional Gastrointestinal Disorders. Curr Gastroenterol Rep.2017;19(10): 53.
11. Akbar A, Walters JR, Ghosh S. Review article: visceral hypersensitivity in irritable bowel syndrome:molecular mechanisms and therapeutic agents. Aliment Pharmacol Ther.2009;30(5):423-435.
12. van Tilburg MAL. Can we treat visceral hypersensitivity in functional abdominal pain? Lancet Gastroenterol Hepatol.2017;2 (10):694-695.
13. Yi L, Sun H, Ge C, et al. Role of insular cortex in visceral hypersensitivity model in rats subjected to chronic stress. Psychiatry Res.2014;220(3):1138-1143.
14. Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: a psychoneuroendocrine rationale for stress management in pain rehabilitation. Phys Ther.2014;94(12):1816-1825.
15. Frøkjaer JB, Bergmann S, Brock C, et al. Modulation of vagal tone enhances gastroduodenal motility and reduces somatic pain sensitivity. Neurogastroenterol Motil.2016;28(4):592-598.
16. Chen X, Luo Q, Yan X, et al. Vagal Transient Receptor Potential Ankyrin 1 Mediates Stress-exacerbated Visceral Mechanonociception After Antral Cold Exposure. J Neurogastroenterol Motil.2019; 25(3):442-460.
17. Fan J, Wu X, Cao Z, et al. Up-regulation of anterior cingulate cortex NR2B receptors contributes to visceral pain responses in rats. Gastroenterology.2009;136(5):1732-1740.
18. Feng CC, Yan XJ, Chen X, et al. Vagal anandamide signaling via cannabinoid receptor 1 contributes to luminal 5-HT modulation of visceral nociception in rats. Pain.2014;155(8):1591-1596.
19. Yan XJ, Feng CC, Liu Q, et al. Vagal afferents mediate anti-nociception of estrogen in a rat model of visceral pain: the involvement of intestinal mucosal mast cells and 5-hydroxytryptamine 3

signaling. J Pain. 2014;15(2):204-217.
20. Hart A, Kamm MA. Review article: mechanisms of initiation and perpetuation of gut inflammation by stress. Aliment Pharmacol Ther. 2002;16(12):2017-2028.
21. Deiteren A, de Wit A, van der Linden L, et al. Irritable bowel syndrome and visceral hypersensitivity : risk factors and pathophysiological mechanisms. Acta Gastroenterol Belg.2016;79(1):29-38.
22. Xu D, Gao J, Gillilland M 3rd, et al. Rifaximin alters intestinal bacteria and prevents stress-induced gut inflammation and visceral hyperalgesia in rats. Gastroenterology.2014;146(2):484-496.
23. Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. Gut.2005;54(10):1481-1491.
24. Chen SL. A review of drug therapy for functional dyspepsia. J Dig Dis.2013;14(12):623-625.
25. Luo QQ, Chen SL. Use of neurotransmitter regulators in functional gastrointestinal disorders based on symptom analysis. J Dig Dis. 2017;18(4):203-206.