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Hong-Yan Qin
First Hospital of Lanzhou University

Chung-Wah Cheng
Hong Kong Baptist University

Xu-Dong Tang
China Academy of Chinese Medical Sciences

Zhao-Xiang Bian
Hong Kong Baptist University, bzxiang@hkbu.edu.hk

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Impact of psychological stress on irritable bowel syndrome

Hong-Yan Qin, Chung-Wah Cheng, Xu-Dong Tang, Zhao-Xiang Bian

Hong-Yan Qin, Department of Pharmacy, First Hospital of Lanzhou University, Lanzhou 730000, China
Hong-Yan Qin, Chung-Wah Cheng, Zhao-Xiang Bian, Lab of Brain and Gut Research, School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong
Xu-Dong Tang, China Academy of Chinese Medical Sciences, Beijing 100700, China
Author contributions: Qin HY wrote the manuscript about experimental evidence; Cheng CW contributed to the manuscript writing on clinical evidence; Tang XD contributed to the structure design of the manuscript; Bian ZX designed the aim of the editorial and finalized the manuscript.
Correspondence to: Zhao-Xiang Bian, MD, PhD, Professor, Lab of Brain and Gut Research, School of Chinese Medicine, Hong Kong Baptist University, No 7 of Baptist Road, Kowloon Tong, Hong Kong. bzxiang@hkbu.edu.hk
Telephone: +852-34112905 Fax: +852-34112929
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Abstract

Psychological stress is an important factor for the development of irritable bowel syndrome (IBS). More and more clinical and experimental evidence showed that IBS is a combination of irritable bowel and irritable brain. In the present review we discuss the potential role of psychological stress in the pathogenesis of IBS and provide comprehensive approaches in clinical treatment. Evidence from clinical and experimental studies showed that psychological stresses have marked impact on intestinal sensitivity, motility, secretion and permeability, and the underlying mechanism has a close correlation with mucosal immune activation, alterations in central nervous system, peripheral neurons and gastrointestinal microbiota. Stress-induced alterations in neuro-endocrine-immune pathways acts on the gut-brain axis and microbiota-gut-brain axis, and cause symptom flare-ups or exaggeration in IBS. IBS is a stress-sensitive disorder, therefore, the treatment of IBS should focus on managing stress and stress-induced responses. Now, non-pharmacological approaches and pharmacological strategies that target on stress-related alterations, such as antidepressants, antipsychotics, miscellaneous agents, 5-HT synthesis inhibitors, selective 5-HT reuptake inhibitors, and specific 5-HT receptor antagonists or agonists have shown a critical role in IBS management. A integrative approach for IBS management is a necessary.

Key words: Psychological stress; Irritable bowel syndrome; Microbiota-gut-brain axis; Immune activation

Core tip: Evidence from both clinical and experimental studies showed that psychological stress, acute or chronic, occurring in early life or adulthood, has marked impact on intestinal sensitivity, motility, secretion and permeability, and the underlying mechanism has a close correlation with mucosal immune activation, alteration in central nervous system, peripheral neurons and gastrointestinal microbiota. This review provides an overview about how psychological stress contributes to the development of irritable bowel syndrome (IBS) and aggravation of IBS symptoms, and informs a more comprehensive approach to the management of IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is a chronic continuous or remittent functional gastrointestinal (GI) disorder affecting, statistically, 11.2% of the global population[1]. It is characterized by abdominal pain or discomfort associ-

ated with a change in consistency or frequency of stools but without gross abnormalities[2]. The pathophysiology of IBS is still inadequately understood, but it is most likely due to complex interactions between the immune, hormonal and nervous systems[3]. Diverse factors, including psychological stress, food intolerance or allergy, intestinal infection, injury (*e.g.*, abdominal or pelvic surgery), intestinal immune disruption and/or inflammation, changes in the intestinal microbiota or bacterial overgrowth, and genetic transmission, abuse and early life learning, have been found to contribute to the development of IBS syndrome according to the research in the last decade[4,5].

Recently, disturbance of the bidirectional brain-gut axis is increasingly recognized as a conceptual model of IBS pathophysiology, involving abnormal function in the enteric, autonomic and/or central nervous systems[6]. As stress can result in overactivity or underactivity along the hypothalamic-pituitary-adrenal (HPA) axis and of the autonomic nervous (ANS), metabolic, and immune systems, it can alter brain-gut interactions, ultimately affecting different physiological functions of the gastrointestinal tract[7]. The relationship between psychological stress and visceral hypersensitivity has been studied and well described by Musial *et al*[8] and Larauche *et al*[9], so this review will not cover that aspect of this topic. The purposes of this review are (1) to provide an overview of how psychological stress contributes to the development of IBS and aggravation of IBS symptoms; and (2) to inform a more comprehensive approach to the management of IBS.

PSYCHOLOGICAL STRESS AND STRESS-ACTIVATED PATHWAYS

Stress as a specific medical term was first defined by the endocrinologist Hans Selye in 1936[9] as the physiological adaptive responses to perceived (psychological) or real (physical) threats ("stressors") to an organism[7,9]. An acute (sudden or short-term) stressor can evoke a "fight or flight" response that prepares to defend the stability of the internal environment in order to ensure the survival of the organism. When the stress passes, a negative feedback is triggered to terminate the stress response and bring the body back to a state of homeostasis or eustasis[10]. However, if the stressor becomes chronic and/or exceeds the organism's ability to maintain the stress response, it becomes harmful because basal homeostasis cannot be reached[9]. For most humans in modern societies, psychological stress is more frequent than physical stress and it may be induced by various social and emotional triggers, some of which can be unique for an individual.

In the stress-activated pathways, the corticotrophin releasing factor (CRF) signaling system is a key element in the biochemical mechanism by which the brain translates a stimulus into an integrated physical response[10]. This system is composed of the 41 amino acid peptide, three related peptides, namely urocortin 1, urocortin 2 and urocortin 3, as well as the CRF receptors CRF1 and CRF2 and their variants[9]. When the body experiences stress, the CRF signaling system plays a primary neuroendocrine role in stimulating the HPA axis, acting as a neurotransmitter/neuromodulator to coordinate the immune and visceral efferent limbs, and activating the locus coeruleus and its noradrenergic projections. The CRF system can also modulate the forebrain, hindbrain and spinal sites for regulating the autonomic nervous system activity, leading to the stimulation of the sympathetic nervous system, release of catecholamines and induction of sacral parasympathetic activity[10]. In addition, stress affects directly or indirectly the composition and the growth of microbiota, which helps to maintain bidirectional communication between the components of the brain and the gut axis[7]. The impact of stress on the brain-gut axis has been reviewed by Grenham *et al*[11] and O'Malley *et al*[12].

Cellular effectors are also considered to play an important role in stress-induced alterations of the gut. These factors include mast cells, enterochromaffin (EC) cells, and lymphocytes, as well as the neurotransmitters, *e.g.*, proteases, 5-HT, and pro-inflammatory cytokines. It is well known that mast cells, EC cells and lymphocytes located in the lamina propria and mucosa constitute the major subpopulation of mucosal leukocytes which are involved in mucosal innate immunity against alimentary allergens and infections. Immune activation has been observed more frequently in IBS patients than in healthy controls. A wide array of mediators released by immune cells in IBS patients have been found to evoke peripheral sensitization of mucosal neuronal afferents and recruitment of "silent" nociceptors[13,14]. Moreover, at the cellular level, immune cells are known to express receptors for several different stress-related peptides including CRF, and the CRF family of peptides has potent immunomodulatory actions, suggesting that there may be crosstalk between stressors and immune factors in IBS[12].

The role of intestinal microbiota in the pathogenesis of IBS has drawn much attention in recent years. As a natural reservoir of microbiota, the GI tract plays a physiological role in metabolic, protective and structural functions in the body, while dysbiosis may contribute to several diseases, including IBS[15]. Chronic stress can induce dysbiosis and enhanced bacterial wall adherence, while the interaction between host and microbiota can modulate the neuro-immune-endocrine systems[16], suggesting that stress-induced microbiota alteration of the gut also plays a critical role in the pathogenesis of IBS. It has been reported that the abnormal GI microbiota interacts with the immune system and nervous system, which may cause the GI tract dysfunction by disturbing the brain-gut axis[17]. Now, the emerging concept of a microbiota-gut-brain axis suggests that targeting the gut microbiota may be a viable approach to treating complex disorders of the central nervous system[18].

Stress stimulates the HPA axis and then triggers the

release of CRF, ACTH, and cortisol, which directly or indirectly affect gut function, influences the composition and the growth of microbiota, and also stimulates the sympathetic nervous system. Stress alters the quantity of mast cells, EC cells, lymphocytes as well as their produced neurotransmitters, which are all involved in mucosal immune activation and further interact with gut microbiota and gut function. Stress-related changes in gut microbiota help maintain contact between the brain and gut.

PSYCHOLOGICAL STRESS IN IBS DEVELOPMENT

Evidence from clinical research

The co-morbidity of IBS and psychological distress is common, and the prevalence of at least one psychiatric disorder typically ranges from 40% to 60% and has been reported as high as 80%[19,20]. A strong correlation can also be observed between the severity of IBS and its co-morbid psychiatric disorders, especially depression and anxiety[12,19]. One review about the psychosocial determinants of IBS published in 2013[21], reports a significant increase in stressor score just before progression from IBS non-patient to IBS patient. And also major life traumas (*e.g.*, disruption of a close relationship, a marital separation, a family member leaving home, or break-up of a serious girl/boyfriend relationship) were frequently reported 38 wk prior to onset of IBS symptoms. In addition, other previous studies have demonstrated that early adverse life events (EALs) are associated with the prevalence of IBS[22,23]. EALs refer to traumatic experiences during childhood (*e.g.*, maladjusted relationships, severe illness or death of a parent, and physical, sexual or emotion abuse). In patients, the occurrence of IBS is typically associated with a higher total early life trauma score and impacted on health related quality of life (HRQOL)[22]. These studies strongly and clearly suggest that psychological or psychosocial stressors determine the development of IBS.

At the same time, there is some conflicting evidence about the relationship between stress and severity of IBS. In his review, Surdea-Blaga *et al*[21] showed that stressful life events can exacerbate abdominal pain and abdominal distension in up to one-third of IBS patients. In contrast, Blanchard *et al*[24] showed that the relation between stress and IBS symptoms was in a reciprocal, not causal, relationship after studying 254 treatment-seeking IBS patients for 4 wk. In yet another cross-sectional study of 153 consecutive patients diagnosed with different IBS subtypes (*i.e.*, constipation-predominant, diarrhea-predominant and mixed), Farzaneh *et al*[25] found no significant difference in the psychological profiles.

Evidence from animal studies

Based on the stress-related modulation in IBS patients, different experimental animal stress models have been developed to assess the vulnerability, the triggering and perpetuating factors determining stress. These include: an acute/chronic mild stress model with exposure to water avoidance stress; neonatal maternal separation stress model; restraint stress, genetic models of chronic stress, post-traumatic stress disorder model, neonatal inflammation/neonatal pain models, post-infectious IBS model and post-inflammatory IBS model. They provide a variety of approaches to explore hypotheses regarding the pathophysiological mechanisms underlying stress-related modulation of pain, visceral sensation and motility[9,10].

Experimental studies have shown that mucosal mast cells are activated after acute stress, and that they are increased or located closer to enteric nerves after chronic stress[26-28]. These mast cells release neuropeptides, *i.e.*, 5-HT, proteases and pro-inflammatory cytokines, known to be the mediators responsible for the altered intestinal sensation, motility, secretion and permeability characteristic of IBS[29]. As the majority of enteroendocrine cells, intestinal EC number and its product 5-HT content are elevated after early life stress (neonatal maternal separation)[30-32], and the increased 5-HT has been confirmed to have close correlation with the symptom generation of IBS[33,34]. In addition to mast cells and EC cells, the increased numbers of immune cells, such as T cells, with production of various cytokines are observed in the intestinal mucosa, which may be responsible for the immune activation in IBS. Dysfunction of the intestinal barrier, such as increased intestinal permeability and reduced intestinal blood flow, can be caused by different types of stress and the underlying mechanism was found to have a correlation with release of acetylcholine, glucocorticoids and corticotrophin-releasing hormone, activation of intestinal mast cells, and even splanchnic vasoconstriction driven by activation of the parasympathetic nervous system[35]. Intestinal barrier dysfunction may cause local or systemic inflammatory reactions and immune activation, which further affect the neuroendocrine-immune pathways and lead to abnormal GI function. It is becoming well recognized that low-grade inflammation and the activated innate and adaptive immune responses play a vital role in the pathogenesis of IBS[36,37]. Now, psychological stress was found to mediate the immune activation and alter the body's responses to stress, which may facilitate the immune activation and/or exacerbate the dysregulation of stress response in IBS, and thus cause symptom flare-ups or exaggeration[12].

Besides the gut, early life stress also has an impact on the central nervous system and peripheral neurons. For example, stress up-regulates the tyrosine kinase receptor A nociceptive fibers, *c-fos* expression and CRF expression in the spinal cord and brain[38-40]; while stress down-regulates voltage-gated potassium channels and up-regulates sodium channels in colonic DRG neurons[41,42]. All of these factors contribute to the altered visceral hypersensitivity in IBS. It is found that both chronic water avoidance stress and acute restraint stress can increase colonic motility and induce sustained visceral hyperalgesia in rats, and CRF has been reported to be the key

factor responsible for stress-induced intestinal dysfunction[43,44]. In recent years, the fecal microbiota was also found altered in the rats exposed to early life stress, and gastrointestinal microbiota has been considered to play an important role in the pathogenesis of IBS[45,46].

The above experimental evidence from animals shows that stress, acute or chronic, applied in early life or adulthood, has marked impact on intestinal functions, and that the underlying mechanism has close correlation with alterations in mucosal immune cells, the central nervous system, peripheral neurons and gastrointestinal microbiota. The strong linkage of psychological stress and IBS originates from the brain-gut axis. Under normal conditions, the brain (central nervous system) communicates with the gut (enteric nervous system). The enteric nervous system (also named as "little brain") plays an essential role in the regulation of gut physiology, including secretion, motility and release of various neuropeptides and hormones[7]. Stress can induce alternations in central stress and arousal circuits (emotional motor system), result in increased CRF and noradrenergic release and activation of behavioral and autonomic responses. These may disrupt the sympathetic and parasympathetic nervous systems, HPA axis, endogenous pain modulation systems, and ascending aminergic pathway[22].

In fact, the communication between the central nervous system and enteric nervous system can be two-directional; whereas the brain can influence the function of the enteric nervous system. Therefore, stress can be the etiology for the development of IBS or aggravation of IBS symptoms (top-down model). IBS symptoms (*e.g.*, chronic continuous or remittent abdominal pain or discomfort associated with a change in consistency or frequency of stools) can elucidate or aggravate psychological disorders (*e.g.*, depression and anxiety) and lower the health related quality of life (bottom-up model). Combination of the both top-down and bottom-up models is also available for this bi-directional mechanism[47].

MANAGEMENT OF IBS

There is strong evidence that IBS is a stress-sensitive disorder. Therefore, the treatment of IBS should pay much attention to managing stress and stress-induced responses. Due to the failure of traditional pharmaceuticals, *e.g.*, laxatives and secretagogues, to give permanent relief, non-pharmacological approaches are now getting more and more attention. They include physician-patient relationship and placebo, patient education, utility of hypnotherapy, cognitive behavioral therapy, dietary modification including probiotics, exercise, and biofeedback[48]. Furthermore, a growing body of experimental data and clinical observations indicate the existence of a three-limbed microbiota-gut-brain axis. This is worthy of much further investigation for the development of any microbiota-based and microbiota-specific therapeutic strategies for IBS in the future. Moreover, pharmacological elements targeting GI symptoms and psychological symptoms should be developed further to treat the irritable bowel and irritable brain.

It is well known that 5-HT plays a critical role in stress-related alteration of gut motility, visceral sensitivity, and intestinal secretion, and also in the pathophysiology of many extra-intestinal stress-related disorders, such as anxiety, depression or chronic pain syndrome[9]. Therefore, therapeutic strategies that target 5-HT availability has been studied extensively, such as the inhibitor of 5-HT synthesis enzyme (tryptophan hydroxylase, TPH), selective 5-HT reuptake inhibitors, 5-HT-norepinephrine reuptake inhibitors, 5-HT3 receptor antagonists, and 5-HT4 receptor agonists have been investigated and some of them have been applied clinically to relieve symptoms of IBS. LX1031, an locally acting, small molecule inhibitor of TPH, has been confirmed to relieve symptoms and increase stool consistency in non-constipating IBS patients in a phase 2 study[49]. Alosetron, a representative antagonist of 5-HT3 receptors, is an effective agent in the symptom improvement of diarrhea-predominant IBS, but the serious adverse effects (*i.e.*, constipation and ischemic colitis) made it only being used under restrictive guideline. Tegaserod, a selective partial agonist of the 5-HT4 receptor, improved bowel habit but not abdominal pain in IBS patients, but the possible cardiovascular adverse effects made it being withdrawn. Nowadays, strategies targeting serotonergic systems remain active, 5-HT4 agonists, *i.e.* prucalopride, ATI-7505 and TD-5108, have been reported to have selectivity for 5-HT4 and will be advanced to human trial[50]. Ramosetron, a 5-HT3 receptor antagonist, was found effective in the treatment of visceral pain in IBS patients[51].

The pharmacological approaches for stress-related disorders also include tricyclic antidepressants, atypical antipsychotics and some miscellaneous agents[20]. Thorough development and assessment from the brain-gut aspect will provide more solid evidence about their usage in IBS patients.

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P- Reviewer: Chen JX, George V, Liu ZJ, Stasi C, van Tilburg MAL
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