ROLE OF STRESS IN PATHOPHYSIOLOGY OF IRRITABLE BOWEL SYNDROME

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ABSTRACT
Stress has been implicated as an important factor in the onset and exacerbation of wide array of disorders, from depression to irritable bowel syndrome. Stress results in the activation of hypothalamic pituitary axis (brain-gut axis) which releases corticotrophic releasing hormone. Corticotrophic releasing hormone released from hypothalamus secretes cortisone into blood which is a stress hormone, which alters visceral hypersensitivity, gastrointestinal motility, gut microflora, immune system and psychological action. As the pathophysiology and causes of IBS are not well understood, treatment focuses on symptomatic management to maintain everyday functioning and improve quality of life for patient with IBS. This review provides an overview on the impact of stress and causes of irritable bowel syndrome.

KEY WORDS: Stress, hypothalamic pituitary axis, corticotrophin releasing hormone.

INTRODUCTION
Irritable bowel syndrome (IBS) is a highly prevalent gastrointestinal disorder characterized by abdominal pain and discomfort in association with altered bowel habits. It is estimated to affect 10%-15% of the Western population, and has a large impact on quality of life and direct healthcare costs1. The causes of IBS are not well understood, but are believed to be multifactorial. It is one of the most prevalent disorder encountered by gastroenterologists and also one of most common gastrointestinal disorders managed by general practitioners. Despite being very common, the pathophysiology of IBS is incompletely understood, which poses problems in the search for effective therapeutic alternatives. Altered psychosocial function, disturbed gastrointestinal (GI) motility and visceral hypersensitivity are considered to be important mechanisms involved in the pathophysiology of IBS2. The early environment has a great impact on the development of behavioral and hormonal responses to stress and events interrupting this development, such as adverse early life events, are associated with a abnormal stress response system which might increase vulnerability to disease3.

The stress is generally considered as the functional adaptation of the organism to cope with a changing and challenging environment. Thus, exposure to a stressor is immediately followed by somatic and neurophysiological reactions involving peripheral organs (such as adrenals, cardiovascular and respiratory systems, metabolism), and brain areas. In laboratory conditions, the most commonly used stressors are restraint or immobilization, forced swim and inescapable footshocks4. Recent findings reveal that IBS can result in dysregulation of brain-gut axis. The axis connecting the brain and gut involves a complex interaction of neural, immune and endocrine pathways which could be affected by various stressors leading to its dysregulation5. The brain and gut axis consist of central nervous system (CNS), autonomic nervous system (ANS), and enteric nervous system (ENS). The ANS comprises of sympathetic and parasympathetic neurons, whereas the ENS comprises the neurons controlling motor and sensory function within the gut wall. Parasympathetic neurons of the ANS are responsible for stimulating gastrointestinal activity, thus playing important role in defecation. They also serve as a connection between the motor and sensory pathways of ENS and CNS. Sympathetic neurons of the ANS are responsible for stimulating gastrointestinal activity, thus playing important role in defecation. They also serve as a connection between the motor and sensory pathways of ENS and CNS. Sympathetic neurons of the ANS decrease GI activity and play a role in sensation. The gut is innervated extrinsically by the parasympathetic and sympathetic neurons of the ANS. However, the gut also contains an intrinsic pathway that is capable of working independently of the brain. A disruption in either the intrinsic or extrinsic pathway of the gut may lead to development or worsening of GI symptoms6.

Stress is characterized by physiological changes that occur in response to novel or threatening stimuli. The adrenal gland is an essential stress-responsive organ that

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is part of both the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenergic system⁷. Stressful events can activate hypothalamic -pituitary-adrenal axis (HPA) and trigger the release of corticotropin releasing factor (CRF) from hypothalamus, this in turn stimulates the secretion of adrenocorticotropic hormone (ACTH) from anterior pituitary, along with secretion of glucocorticoids (corticosterone) from adrenal cortex into circulatory system. Cortisone released from adrenal cortex affects metabolic actions, immune response, locomotion, sexual behavior and learning, in IBS patients⁸. Activation of sympathetic-adrenergic system, results in the “fight or flight” response due to the release of catecholamines from the chromaffin cells of the adrenal glands. The central and peripheral pathways of brain-gut axis which could mediate the symptoms of irritable bowel syndrome are shown in fig.1. 

CRF is one of the principle effectors of stress responsive system that is released in the brain in response to stressors and play pivotal role in activating HPA⁷. In addition to role of CRF in altering gastrointestinal motility, it is also involved at the central nervous system level in the modulation of visceral pain. This effect of central CRF is linked to the peripheral activation of mast cells within the GIT, sensitizing mechanoreceptors in the GIT or promoting mast cell degranulation in response to distension⁹. Biological actions of CRF are mediated through two CRF receptor subtypes CRF-R1 and CRF-R2, both being expressed in the gastrointestinal tract¹⁰. These receptors are G protein coupled receptors signaling through cAMP synthesis. CRF can be peripherally synthesized in colonic mucosal cells and its local release can modulate intestinal immune system and other gastrointestinal functions¹¹.

In several tissues, CRF signaling promotes immune response and stimulates human lymphocyte proliferation by increasing IL-2 (interleukin) receptor expression and enhancing the production of IL-1α and IL-2¹². In addition to this, CRF also enhances the:

a) Endotoxin induced cytokine release (Tumor necrosis factor-α, IL-1α and IL-6) from the peritoneal macrophages;

b) Chemotaxis of mononuclear cells and;

c) Induces macrophagic activation which is associated with local release of oxidative mediators and pro-inflammatory cytokines¹³.

Recently, investigators have hypothesized that IBS is caused by a defect in enteric nervous system (ENS). The ENS controls motility and secretory functions of the intestine. It is a semiautonomous system that can function independently or have its actions modified by the sympathetic or parasympathetic nervous system. The ENS contains many neurotransmitters, including serotonin, substance P, vasoactive intestinal peptide, and calcitonin gene related peptide. Defects in the ENS may lead to the symptoms of IBS characterized by visceral hypersensitivity and primary motility disorder of GI tract¹⁴. Mast cells play a critical role in the regulation of epithelial transport both in human¹⁵ and rodent intestine¹⁶ and is widely accepted that nerve mast cell interactions are involved in intestinal epithelial dysfunction¹⁷. Nerves and mast cells participate in the development of stress-induced increase of colonic paracellular permeability.

Effects of stress on behavior are complex, and depend on the time of exposure to the stressor and gender. Repeated exposure to the same stress event can lead to a process of adaptation to that stimulus. Hence, chronic stress does not show the same behavior and do not experience the same extent of consequences as that of the animals exposed to acute stress. For example, repeated exposure to stress situations has been shown to modify the behavioral response to opioid and physiological responses to cholinergic administration. Different neurotransmitter systems have been suggested to play a role in this stress desensitization process, such as adaptive changes on monoaminergic sites, opioid modulation, gabaergic and cholinergic function¹⁸. Recently various stressors have been associated with enhanced free radical generation causing oxidative stress. The first event and one of the most important consequences of free radical production is the membrane lipid peroxidation. Moreover, stress has been suggested to decrease the levels of glutathione (GSH) and vitamin C and, both substances that play an important role in tissue protection from oxidative damage. Acute stress induced by sleep deprivation has been shown to increase the levels of lipid peroxidation indicators and to produce a decrease in antioxidant enzymatic activities and glutathione levels¹⁹.

**FACTORS INVOLVED IN PATHOPHYSIOLOGY OF IRRITABLE BOWEL SYNDROME**

Impact of stress on following factor is shown in fig. 2.

**Visceral hypersensitivity**

Visceral hypersensitivity in response to colorectal distension is a hallmark feature of irritable bowel syndrome and is claimed to be present in 50–90% of the patient population. Visceral hypersensitivity is one of the most commonly reported pathophysiological alterations, usually assessed with balloon distensions and it is a feature found throughout the entire GI tract of IBS patient. Rectal hypersensitivity has been proposed to be a biomarker for IBS and is useful to discriminate the disorder from other causes of abdominal pain²⁰.
Increased visceral sensitivity in patients with IBS was first observed in the colon by Ritchie in 1973. Visceral hypersensitivity is caused by different factors involving both the peripheral and central nervous system. Afferent nerves transmit the visceral sensations arising from gastrointestinal tract to the spinal cord and the brain, where pain and discomfort are perceived. These signals could be amplified at different levels such as gut, spinal cord or brain leading to a significant increase in brain response as observed in IBS patients. On the other hand, descending inhibitory mechanisms which control visceral signal transmission from the periphery to the central nervous system can be altered. Involvement of central and enteric nervous system in altering intestinal motility and visceral hypersensitivity is shown in fig. 3. To support the role of peripheral mechanisms, it has been demonstrated that:

(i) IBS occurs more frequently after irritation of the gut by infectious agents,
(ii) Infiltration of inflammatory cells that take place near the enteric plexus,
(iii) Pain hypersensitivity is found only in the visceral but not in somatic system of IBS patients.

It is proven that IBS patients are hypersensitive to visceral stimuli, but visceral sensitivity might not present in all patients. Differences in visceral hypersensitivity in patients is based upon the predominant bowel habit that is IBS-Constipation or IBS-Diarrhea, as well as gender 21.

**Gastrointestinal motility**

Stress is a major contributing factor in the pathogenesis of IBS and can increase the colonic motility in patients with IBS. Central corticotropin-releasing factor (CRF) released by stress accelerates colonic transit and defection via stimulation of vagal efferent nerves which can be abolished by systemic treatment with 5-HT3 receptor antagonists. Disorders of colonic transit may contribute to symptoms of constipation and diarrhea predominant IBS. A number of motility alterations have been seen and described in IBS patients. It has been related to the occurrence of abnormal colonic and intestinal contractions in IBS and the most important motor alterations in colonic motility include exaggerated motor response to emotional stress, CRH, cholecystokinin (CCK), increased frequency motor response to emotional stress, CRH, enterogastrone and defecation in several species including gerbils, rats and humans. Stress-induced colon motility is increased in irritable bowel syndrome patients 23.

**Gastrointestinal inflammation**

Inflammation is associated with the production of mediators that can induce changes in visceral perception, motility and secretion. Recent evidence suggests that transient or chronic inflammation play a important role in IBS pathogenesis. There is an evidence for intense local immune response, associated with recruitment and activation of lymphocytes and macrophages in IBS. These cells are activated and release several mediators like interleukin, nitric oxide, histamine and proteases, which are capable of stimulating the enteric nervous system resulting in the abnormal secretion and motor response in the gut. The subsequent release of soluble cytokines and other inflammatory mediators causes tissue damage and contributes to many of the clinical features of these diseases and to the amplification and perpetuation of the local immune response 24.

Role of stress in altering neurotransmitter release which further brings inflammatory changes to increase the symptoms of irritable bowel syndrome that is shown in fig. 4. Activation of mucosal immune system in IBS increases mucosal mast cells along with their degranulation rate, which play important role in severity of IBS symptoms. Increased infiltration of mast cells has been seen throughout the GI tract of IBS patients which provide evidence on immune cell activation in IBS 25.

Neonatal maternal deprivation (NMD) predispose to colonic barrier dysfunction 5 and enhance mucosal response to mild stress 26. There is an increase in mast cell number and proteinase-activated receptors (PAR-2) expression in the colon under stressful conditions and these alterations can lead to increased intestinal permeability, inducing inflammation and hypersensitivity of the intestine which can be inhibited by the CRF antagonist astressin 22.

**Neuropeptides**

There is a growing evidence that both stress and anxiety are associated with the release of neuropeptides as secretogogues of various effector cells which, in turn, secrete pruritogenic and proinflammatory mediators. Cholecystokinin (CCK) is the principal physiological “enterogastrone” involved in the control of gastric acid secretion, gastric emptying, gastrointestinal motility,
food intake and gastric mucosal integrity. Furthermore, CCK-8 reduces the magnitude of gastric injury caused by exposure to luminal irritants suggesting that this protective action may have a physiological significance.28

Gut Microflora

The bacterial composition of intestinal flora plays an important role in both maintaining good health and development of disease states such as IBS. The human gastrointestinal tract is a complex ecosystem whose maintenance depends on the physiological functions of the host, particularly the co-operation between the mucosal barrier and local immune system. Over 300,000 bacterial genes circulate in human gut.21 The stomach and the proximal small bowel contain normally only a few species of bacteria, particularly Lactobacilli and Enterococci. Bacterial density rises towards the colon, reaching concentrations up to 10^{12} Colony-Forming Units (CFU) per ml. The symbiotic relationship between microbiota and gut is important for the integrity and function of the gastrointestinal tract and involves a continuous and dynamic effect on the host. In fact, the intestinal microflora plays a role in defense against pathogenic organisms, in the regulation of metabolic and trophic functions of epithelial cells and in the synthesis of vitamins and nutrients. It also exerts remarkable effects on the development and maintenance of gut sensory and motor functions, including the promotion of intestinal propulsive activity. Fecal samples from IBS patients show different number of bacterial strains and greater instability in composition of their intestinal microflora over time. Use of antibiotics cannot be regarded as safe in IBS since antibiotics may worsen symptoms of IBS by altering the delicate balance between ‘good’ and ‘bad’ bacteria in the gut.29

Genetic factors

Many data suggest the important role of genetic factor in IBS. Patient having family history of IBS will be more susceptible to disease. Recent studies has lead to identification or involvement of polymorphism of a gene expressing IL-10, TNF-α in controlling down regulation of inflammation and serotonin metabolism.31 Genetic factors alone cannot explain IBS but an interaction between environmental and genetics factors can lead to the clinical symptoms of the disease. To date, more than 100 genetic variants in more than 60 genes from various pathways have been studied in a number of candidate gene studies, with several positive associations reported.21

Psychological stress

Psychological stress stimulates colon motility in several species including man.23 The acute and/or chronic psychological stress produce changes in urinary bladder nociception. The chronic psychological stress significantly enhances bladder nociceptive responses only in high-anxiety rats and thus supports the critical role of genetics, stress and anxiety as exacerbating factors in painful urogenital disorders.32 Psychological factors including fatigue and depression are associated with low grade inflammatory infiltrate and increased mast cell count in biopsies of the colon of IBS patients.33

CONCLUSION

Irritable bowel syndrome can induce significant disturbances and could be catalyzed largely by stress related factors. The blunting of HPA axis together with alterations in sympathetic modulation of immune function may predispose individuals to develop IBS. CRF signaling in the brain, established a leading mediator of the biochemical effect on the endocrine and anxiogenic behavior responses to stress, is also a part of the underlying mechanisms through stress inhibits gastric transit and stimulates colonic transit in experimental animals. These data support the involvement of the CRF system at the central or peripheral sites as part of the mechanisms where by stress triggers or enhances gut complaints in patients with IBS. The pathogenesis of IBS has to be carefully evaluated in order to develop strategies for the management of IBS.

REFERENCES

10. Chatzaki E, Crowe PD, Wang L, Millon M, Tache Y, Grigoriadis DE. CRF receptor type1 and 2 expression and
Fig 1. The central and peripheral pathways of brain-gut axis which could mediate the symptoms of irritable bowel syndrome.

Fig 2. Impact of stress on following factors:
- Visceral hypersensitivity
- Gastrointestinal motility
- Hormones and neuropeptides
- Gastrointestinal inflammation
- Gut microflora
- Psychological stress

Fig 3. Involvement of central nervous system and enteric nervous system in altering intestinal motility and visceral hypersensitivity.
Fig. 4 Role of stress in altering neurotransmitter release which further brings inflammatory changes to enhance the symptoms of irritable bowel syndrome.