

BIOLOGICAL INTERACTION OF STRESS AND IRRITABLE BOWEL SYNDROME

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ABSTRACT

A variety of stressors play a role in the development of irritable bowel syndrome. Irritable bowel syndrome is a biopsychosocial disorder that results from dysregulation of central or enteric nervous system function. The physiological effects of psychological and physical stressors on gut function and brain-gut interactions are mediated by outputs of the emotional motor system in terms of autonomic, neuroendocrine, attentional, and pain modulatory responses. Certain investigational studies reported to date indicate that the activation of CRF1 pathways may result in a combination of effects that are key features of symptoms in some irritable bowel syndrome patients. These include stimulation of colonic motility, defecation or watery diarrhea, gut hypersensitivity that increases the perception of stimuli within the bowel, focused attention (hypervigilance) toward the gut sensations, and mast cell activation. Blocking the CRF1 receptors may alleviate all these effects. Stress thus can be included in an integrative model explaining the pathophysiology of functional bowel disorder. Advances in the understanding of the relationship between stress and visceral perception may constitute a basis for a therapeutic approach of functional bowel disorders targeted on the central nervous system.

Key Words: Stress; GI Activity; Corticotropin Releasing Factor; Irritable Bowel Syndrome

Introduction

Irritable bowel syndrome (IBS) is a highly prevalent functional gastro-intestinal disorder affecting predominantly the colon which is mainly characterized by abdominal pain and discomfort in association with altered bowel habits in the absence of any structural abnormalities.^[1] Various stressors in the form of early life trauma, sexual abuse, maternal neglect, fear conditioning, life-threatening events, and enteric infections have an important role in the etiology of IBS.^[2-5] Acute physical and psychological stress alters gut-specific efferent autonomic innervations. However, increased visceral sensation in patients with IBS suggests the involvement of a different regulatory mechanism, either central or peripheral.^[6]

Stress activates different brain regions to coordinate the behavioral and physical changes which allow the organism to adapt. It triggers two main pathways: pituitary-adrenal axis and autonomic nervous system. Pituitary-adrenal axis acts to increase circulating hormones (glucocorticoids – particularly cortisol) which regulates the body's response to stress while later regulates different involuntary bodily functions including the bowel activity. Both of these pathways directly or indirectly affect enteric nervous system and collectively forms brain-gut axis.^[7-9]

Stress induced somatic hypoalgesia mediated by descending pain inhibitory pathways involving

opioidergic, glutaminergic, and serotonergic systems can be accompanied by a stress induced visceral hyperalgesia indirectly mediated by sympathetic and/or parasympathetic nerves stimulating the release of chemicals from mast and enterochromaffin like (ECL) cells within the gut wall which sensitizes the visceral afferent terminals. The net effect of simultaneous activation of both pain facilitatory and inhibitory systems in response to stress is determined by the relative contribution of these opposing influences.^[10-13] Alterations in these endogenous stress activated pain modulation systems may play an important role in several functional visceral or somatic syndromes characterized by chronic discomfort and pain, features of IBS.^[14]

Stress and Gut Function

Various stressors have revealed inhibition of gastric emptying and stimulation of colonic motor function. Activation of brain corticotropin releasing factor (CRF) receptors mediates stress-related inhibition of upper GI and stimulation of lower GI motor function through interaction with different CRF receptor subtypes.^[15-17] Several reports consistently established that CRF injected into the cerebrospinal fluid (CSF) acts in the brain to inhibit gastric emptying of a solid or liquid meal and contractility in rats and dogs.^[18,19] The paraventricular nucleus (PVN) of the hypothalamus and dorsal vagal complex (DVC) are responsive sites for CRF-induced delayed gastric emptying and inhibition of

central vagal stimulation of gastric motility in rats, respectively.^[19] The central mechanism for activation of autonomic effect for the gut function also includes amygdala which is centre to emotional system related to the stress.^[20] The amygdala is an important structure for regulating anxiety with the central nucleus of the amygdala facilitating the activation of the hypothalamic-pituitary-adrenal axis and the autonomic nervous system in response to stress. Moreover, chronic stress enhances function of the mineralocorticoid and glucocorticoid receptor-mediated mechanisms within the amygdala in the regulation of anxiety and nociceptive behaviors that are characteristic features of IBS.^[21]

Though there is a well-defined relationship between the immune and neuroendocrine systems through which immune signals activate the hypothalamic-pituitary-adrenal axis, central CRF-induced delayed gastric emptying is independent from the activation of pituitary-adrenal hormone release.^[22] It is most likely related to the alterations of autonomic nervous system activity, in which the decrease in gastric vagal outflow plays a major role.^[19]

CRF Receptors and Gut Activity

One of the most important discoveries in the last decade in identifying the substances related to stress response is a family of peptides named corticotropin-releasing factor (CRF): urocortin 1, urocortin 2, and urocortin 3. CRF plays a crucial role in the stress-related stimulation of the hypothalamo-pituitary-adrenal axis and, in association with urocortins, acts as a neuromodulator to coordinate the behavioural, autonomic, and visceral efferent limbs of the stress response.^[23-26] These peptides act as messengers and interact with CRF receptors (CRF₁ and CRF₂) located, among other sites, both in the gut and brain regions linked with digestive function, emotional behaviour, and autonomic nervous system activity.^[16] It is increasingly recognized that CRF₁ receptors activated by CRF and urocortin 1 in brain stress network increase the anxiety-like behaviour along with changes in endocrine function and in gut these peptides change the colon functions, such as muscle contractions or motility, secretion and pain sensitivity leading to abdominal pain and development of watery stool or diarrhea.^[17-19] In particular, CRF increases mucus and water secretion into the colon from cells lining the colon wall, and activates the enteric nervous system.^[17]

It is documented that peripheral injection of CRF or

urocortin stimulates colonic transit, motility through Fos gene expression in myenteric neurons, and defecation as a result of CRF₁ receptors activation, whereas it decreases ileal contractility *via* CRF₂ receptors. Some pre-clinical studies have shown that CRF administration into brain mimics acute stress-induced colonic responses and enhances colorectal distension-induced visceral pain in rats through CRF₁ receptors.^[27] Similarly, peripheral CRF reduced the pain threshold to colonic distension and increased colonic motility in humans and rodents. These observations imitate the manifestations of IBS, characterized by abdominal bloating/discomfort and altered bowel habits.^[7,19]

CRF also stimulates mast cells to release substances that play a role in increasing permeability, bacterial uptake from inside the colon to the colonic tissue, and pain response. Similarly, when given CRF, muscle contractions in the colon and pain increases in IBS patients compared to healthy individuals.^[17] Decreased postoperative pain tolerance thresholds were found in patients with increased anxiety. Other compelling animal studies have shown that painful stimulation of the colon activates brain nerve cells through CRF/CRF₁ mechanisms associated with the development of increased vigilance and anxiousness. Therefore, it is conceivable that the increased sensitivity to abdominal pain in IBS patients may cause, in turn, a more pronounced, sustained, and/or frequent activation of CRF/CRF₁ pathways.^[22] CRF₁ antagonist abolished or reduced emotional distress, colonic motility, mucus secretion, mast cell activation, diarrhea, and pain brought on by CRF administration or stress. This also gives evidence supporting the role of CRF pathways in the gut response to stress in IBS patients.^[2]

Indirect pharmacological evidence suggests that intracisternal CRF-induced inhibition of gastric emptying involves interaction with CRF-R2 in rats.^[17,18] Astressin (CRF receptor antagonists) injected into the CSF or the PVN at doses preventing gastric response to centrally injected CRF, block the delayed gastric emptying induced by various forms of stress.^[19] Additionally, intraperitoneal administration of CRF induces colonic mast cells degranulation *via* both CRF₁ and CRF₂ receptors and increases ions secretion and mucosal permeability to macromolecules, which can in turn promote intestinal inflammation and alter visceral sensitivity.^[28] CRF-induced alterations of colonic and ileal functions mimic effects which are observed after stress exposure, and CRF receptor antagonists given

peripherally prevent stress-induced GI dysfunction. Furthermore, CRF peptides can reproduce secretomotor and mucosal alterations *in vitro*.^[29,30] In addition to the brain, a role for peripheral CRF signaling in mediating stress-induced effects on gastrointestinal sensorimotor, mucosal and immune functions, may be components of underlying mechanisms involved in stress-related impact on irritable bowel syndrome.^[1]

Serotonin and IBS

Serotonin (5-hydroxytryptamine [5-HT]), which is produced mainly by and stored in enterochromaffin like cells in the GI tract, is vital to normal gut function such as initiation and maintenance of peristalsis, secretion in the GI tract, and modulation of pain sensation.^[31,32] Recent research has uncovered a potential role for abnormal serotonin expression and/or signalling in IBS and other GI disorders.^[33] The potential effect of sex hormones such as estrogen and progesterone on serotonin remains to be elucidated. A recent study has shown that estrogen and progesterone influence the level of 5-HT type 3 (5-HT₃) receptor mRNA.^[34] In ovariectomized rats, lower levels of prostaglandin and progesterone resulted in significantly higher amounts of 5-HT₃ receptor mRNA. When ovariectomized animals were treated with estradiol and progesterone, 5-HT₃ receptor transcription levels returned to normal. Additional studies highlight the importance of serotonin reuptake transporter in IBS as polymorphisms in this gene resulted in a differential response to alosetron, a 5-HT₃ receptor antagonist that is used to treat diarrhea-predominant IBS.^[35,36] Collectively, these results suggest that 5-HT₃ receptor activity, which is a target of pharmacologic intervention in patients with diarrhea-predominant IBS, is regulated by female sex hormones. However, the importance of serotonin and its receptors, as well as serotonin polymorphisms, in predicting response to treatment remains an area of interest.

Gender, Stress and IBS

In general, more number of women complains of IBS than men. Though the reasons for these gender difference remains elusive, it is explained on behalf of difference in colonic transit time, visceral sensitivity, CNS processing and effect of estrogen and progesterone on gut function, psychological characteristics including somatization, depression, anxiety as well as history of sexual abuse.^[37] A study revealed that the colonic transit time is less in female and lower sympathetic tone.^[38]

Female respond to stress by building attachment and care giving process referred as “tend and befriend” phenomenon mediated by oxytocin and endogenous opioids. This behavioural response may be linked to physiologic response such as down regulation of sympathetic nervous system and HPA axis. On the other hand, male respond with aggressive prototypic fight or flight response, thought to be due to androgen and stress arousal.^[39,40]

Various observations have shown that sex hormone in women has influential role in IBS with report of looser stools, increased bowel symptoms, increased rectal sensitivity during and before menses. GI symptoms increases and intestinal transit decrease during pregnancy.^[41-43] Furthermore, study found that stress-induced visceral hypersensitivity in female rats is estrogen-dependent and mediated through neurokinin (NK1) receptor activation in the colon.^[44,45] Estrogen has direct effect on GI tract calcium dependent potassium channel affecting contractility. In addition, activation of the hypothalamic-pituitary-adrenal (HPA) axis enhances increased activation of the amygdala.^[46] Elevated levels of progesterone and/or estradiol on the amygdala heightened the responsiveness to colorectal distension and thus disproportionately affected by IBS with menstrual cycle.^[47]

Ovariectomy significantly decreases the magnitude of the visceromotor reflex and L6-S1 dorsal horn neuronal activity in response to colorectal distension. The estrogen modulates the spinal cord processing and reflex responses to innocuous and noxious colorectal stimuli in female rats and may contribute to alteration in sensory processing associated with irritable bowel syndrome.^[36]

Conclusion

In summary, these investigational studies reported to date indicate that the activation of CRF₁ pathways may result in a combination of effects that are key features of symptoms in some IBS patients. These include stimulation of colonic motility, defecation/watery diarrhea, gut hypersensitivity that increases the perception of stimuli within the bowel (e.g., food, gas, motor contractions), focused attention (hypervigilance) toward gut sensations, and mast cell activation. Blocking the CRF₁ receptors may alleviate all these effects. Thus, the emerging conceptual framework supports that sustained activation of the CRF₁ system at sites in the brain and/or in the gut may be one component

underlying IBS symptoms. Targeting these mechanisms by drugs that block the action of CRF on selected CRF₁ receptor sites might be a treatment approach to reduce IBS symptoms more effectively.

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