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TOPIC HIGHLIGHT

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Convergence of neuro-endocrine-immune pathways in the pathophysiology of irritable bowel syndrome

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Abstract

Disordered signalling between the brain and the gut are generally accepted to underlie the functional bowel disorder, irritable bowel syndrome (IBS). However, partly due to the lack of disease-defining biomarkers, understanding the aetiology of this complex and multifactorial disease remains elusive. This common gastrointestinal disorder is characterised by alterations in bowel habit such as diarrhoea and/or constipation, bloating and abdominal pain, and symptom exacerbation has been linked with periods of stress, both psychosocial and infection-related. Indeed, a high level of comorbidity exists between IBS and stress-related mood disorders such as anxiety and depression. Moreover, studies have observed alterations in autonomic output and neuro-endocrine signalling in IBS patients. Accumulating evidence indicates that a maladaptive stress response, probably mediated by the stress hormone, corticotropin-releasing factor contributes to the initiation, persistence and severity of symptom flares. Other risk factors for developing IBS include a positive family history, childhood trauma, dietary factors and prior gastrointestinal infection. An emerging role has been attributed to the importance of immune factors in the pathophysiology of IBS with evidence of altered cytokine profiles and increased levels of mucosal immune cells. These factors have also been shown to have direct effects on neural signalling. This review discusses how pathological changes in neural, immune and endocrine pathways, and communication between these systems, contribute to symptom flares in IBS.

Key words: Stress; Corticotropin-releasing factor; Pro-inflammatory cytokines; Enteric nervous system; Vagus

Core tip: Irritable bowel syndrome (IBS) is a disorder characterised by symptoms such as diarrhoea and/or constipation, bloating and abdominal pain. However the underlying pathophysiology of this common disorder remains unclear. Nonetheless, a number of mechanisms have been proposed to contribute to the initiation, exacerbation and persistence of symptoms. Alterations in brain-gut communication, stress, previous infections, abnormal microbiota, altered cytokine profiles and increased intestinal permeability have all been proposed as contributors to IBS and indeed, we propose that complex interactions between neural, endocrine and immune factors underlie the heterogeneity of symptoms that is characteristic of IBS.

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INTRODUCTION

Irritable bowel syndrome (IBS) is the most common functional digestive condition with a worldwide prevalence rate of 10%-20% in the general population[1,2]. As with other functional disorders it is often difficult to identify an unequivocal organic cause, at least with the diagnostic tools available. This disorder accounts for approximately 3% all general practice consultation and up to 40% of gastrointestinal (GI) referrals[3] leading to a large economic burden. At the level of the individual, IBS significantly impinges on the quality of life of a patient causing recurrent abdominal pain or discomfort coupled with disturbed bowel habits[4]. IBS is subtyped according to bowel habit pattern, therefore patients are classified as diarrhoea-(IBS-D) or constipation-predominant IBS (IBS-C) or an alternating subtype (IBS-A), which fluxes between the two states[5]. Some reports suggest that IBS-D and IBS-A are more prevalent[6] while others show an equal distribution between all three subtypes[7]. Although little mortality is associated with IBS a satisfactory treatment still does not exist, primarily due to the fact that the aetiology and pathophysiology of IBS are incompletely understood. Nonetheless, dysfunctional brain-gut axis signalling is hypothesised to be at the heart of symptoms of IBS[8] and this incorporates three major systems, neural, endocrine and immune signalling. In this review we discuss the contribution of each system to IBS symptoms and how convergence and interplay between factors from each system may provide a better understanding of the heterogeneity of IBS.

NEURAL SIGNALLING IN IBS PATHOPHYSIOLOGY

Autonomic regulation of the gut

The two major persisting symptoms of IBS are visceral hypersensitivity and altered bowel habit[9] each of which are entwined within the nervous system. Functions of the GI tract are modulated by both intrinsic and extrinsic innervation[10]. Extrinsic innervation includes both branches of the autonomic nervous system, which are anatomically and functionally integrated within the brain-gut axis and are responsible for homeostatic regulation of GI function[11]. The parasympathetic nervous system stimulates smooth muscle and secretory actions while the sympathetic element inhibits motor and secretory activity of the GI tract. The parasympathetic afferent pathway runs primarily with the vagus and terminates in the nucleus solitary tact, which sends information regarding non-nociceptive information, including gastric accommodation and gastric-colic reflex, to corticolimbic structures[12]. The sympathetic afferent pathways mediates mainly nociceptive signals through spinal pathways primarily to the thalamus and then to the sensory cortex and pain matrix[13]. Information is also sent to specific brain regions such as the hippocampus, amygdala, prefrontal cortex[14] and the hypothalamus[15] for processing. These central regions which are capable of modulating gut function are also involved in emotional (*e.g.* mood, anxiety, pain) and cognitive behaviours (*e.g.* memory, decision making) and hence, in the development of coping strategies and general well-being[16]. A descending pain inhibitory pathway from the brainstem also exists in order to control the signals reaching the brain. The intrinsic or enteric nervous system works somewhat independently providing local reflexes, such as migrating motor complex and peristaltic reflexes, and y*et al*so receives input from the central nervous system (CNS) *via* the autonomic nervous system.

Autonomic dysfunction

A growing body of evidence suggests the existence of autonomic dysfunction in IBS[17-19] and some have shown correlations with symptoms[20]. Low vagal activity can lead to a reduction in bowel contractions, reduced motility, and constipation, while high vagal activity can result in increased contractions and diarrhoea[21]. The sympatho-vagal balance was found to be disturbed in IBS patients compared to healthy controls[22]. Furthermore, a study assessing female IBS patients with constipation and severe abdominal pain showed lower vagal activity than controls[23], which correlates with a study showing an increased parasympathetic tone in women with IBS-D compared to those with IBS-C[24]. Given the close association between the stress axis and the autonomic nervous system, increased sympathetic tone as seen with constipation may be due to the increase in corticotropin-releasing factor (CRF) expression[10], which is discussed in more detail in the next section. Indeed, the psychological disorders that often co-occur with IBS are also associated with altered autonomic balance[25].

Underlying neural causes of visceral hypersensitivity

Visceral hypersensitivity, as seen in a subset of IBS patients, is an exaggerated response to a stimulus such as colorectal distension, was first noted by Ritchie[26], 1973. Several neural theories have been proposed for this increased sensitivity, including sensitisation of primary afferent pathways, increased activity of endogenous pain facilitation and reduced engagement of endogenous pain inhibition[27]. IBS patients have significantly elevated levels of anxiety, interpersonal sensitivity, depression, hostility and somatization of effect, which can impact on pain perception[28]. Some studies indicate a difference in sensitivity to colon and rectal distension between diarrhoea and control subjects[29,30], while patients with constipation showed conflicting results[31,32]. However, a comparison between constipation and diarrhoea predominant IBS patients revealed no significant difference in pain threshold[33].

Peripheral mechanisms-sensitisation of primary afferents

Preclinical studies of acute gut inflammation have shown that sensitization of primary afferent pathways can result in visceral hyperalgesia[34-36]. A subset of IBS patients develop symptoms following an acute GI infection[37]. Usu-

ally peripheral sensitization is temporary and response properties of primary afferents return to normal state after resolution of the inflammation[27]. Evidence from human mucosal biopsies suggests neuroplastic remodelling in the epithelium[38]. Such plastic changes can affect the response properties of primary afferents which include spinal and vagal afferents[39]. Changes in afferent nerve terminals could affect responsiveness to visceral stimuli and interfere with the release of neuropeptides from these terminals resulting in neurogenic inflammation[27].

Central pain amplification

In turn then there are multiple mechanisms by which the CNS can modulate afferent signals from the viscera, including increased activation of endogenous pain facilitation and reduced engagement of endogenous pain inhibition[27]. Of course, these modulatory systems are also influenced by stress and mood[27]. Neuroimaging studies consistently support a role for altered neural processing of visceral stimuli[40]. Indeed, some sophisticated studies now incorporate the contribution of emotional factors and cognitive influences such as expectation, attention and learning, to their analyses of functional connectivity between brain regions and actual CNS structural changes[40].

It was noted that a thinning of the anterior mid-cingulate and insular cortices was evident in IBS patients[41], these areas being associated with perception of the internal state. Moreover, regional structural changes including decreased grey matter in the medial and ventrolateral prefrontal cortex, thalamus and periaqueductal grey are seen in IBS patients as compared to healthy controls[42]. These may point towards an impaired ability to activate the descending pain inhibition system. This hypothesis is supported by the observation that the reduction in grey matter in the ventrolateral prefrontal cortex was only found in the patients presenting with a high level of pain[42]. Central areas involved in the processing of the affective component of pain such as the pregenual anterior cingulate cortex and the orbital frontal cortex showed an increase in grey matter in IBS patients, which was abolished once data was corrected for anxiety and depression in these patients[40]. These findings further confirm the involvement of emotional systems in the processing of visceral pain. Consistent with this, Chen *et al*[43] showed that white matter aberrations are seen in the anterior cingulate cortex and the insula. However, as it is still not known whether these changes are present before symptoms emerge, or are actually acquired due to altered visceral signalling, these results should be interpreted with caution.

Enhanced CNS responses

A meta-analysis of functional magnetic resonance imaging studies in IBS patients reported differences in CNS response to colorectal distension[44]. The differences were seen in areas associated with visceral afferent signalling, attention and emotional arousal. The anterior cingulate cortex is one of the most commonly reported cortical areas that displays pain evoked activation during acute stimulation in patients[43]. Mertz *et al*[45] demonstrated that the anterior cingulate cortex, thalamus, the insula and the prefrontal cortex were more activated in IBS patients than controls and that the pattern of activation was dependent on previous experience. A greater activation of the thalamic, striatal and dorsolateral prefrontal cortex was seen in controls as compared to IBS patients during rectal distension indicating an abnormal descending modulation in IBS[46]. It has also been shown that female IBS patients have a greater engagement of the emotional arousal system during expectation of visceral pain than males[47]. These studies highlight the importance of the emotional status of patients in pain perception and that the female predominance may be in part due to the gender differences in the activation of circuits involved in stress and arousal[27]. Taken together these results indicate a role for both structural and functional abnormalities in the CNS in IBS pathophysiology.

ENDOCRINE PATHWAYS IN IBS PATHOPHYSIOLOGY

CRF

Stress is a pervasive condition that effects everyone and is defined as a "stereotyped body response to any demand"[48]. However, the high co-morbidity of stress-associated mood disorders such as anxiety and depression and altered bowel function in IBS patients[49], suggests that these individuals are more sensitive to the effects of stress. Indeed, the relationship between severe and chronic stress and symptom intensity in IBS patients[50] is linked to chronic stress, with the onset and duration of symptoms increased[51]. As noted above, this may mediated *via* altered autonomic signalling[52], however the key signalling factor initiated by stress is an endocrine hormone, CRF.

CRF is the vital hormone in the body's response to stress, activating the hypothalamic-pituitary-adrenal (HPA) axis in reaction to a variety of physical and psychological stressors. This results in enhanced levels of adrenocorticotropic hormone and cortisol in IBS patients as compared to healthy subjects[53,54]. CRF is secreted by the paraventricular nucleus (PVN) of the hypothalamus and its release is regulated by the amygdala, which is part of the limbic system[51].

CRF exerts its biological effects through activation of CRF1 and CRF2 receptors (CRFR1 and CRFR2), which are members of the seven transmembrane G-protein coupled receptor superfamily[55]. CRFR1 is prevalent in brain regions associated with affective, stress and nociceptive circuitries including the PVN, locus coeruleus and amygdala[56,57]. CRF neurons project from the PVN to the spinal cord, where they can alter the function of innervated organs[58].

CRF in the GI tract

Although much of the influence of CRF on GI function

is mediated centrally, the presence of CRF ligands and its receptors in the colon[55,59,60] suggests that organ-specific activation of these receptors may also be important for stress-induced changes in bowel function. CRFR1 is expressed on enteric neurons and in the mucosal layer[59] and is likely to be the focal mechanism by which stress induces changes in GI function including delayed gastric emptying[61], accelerated colonic transit[62] and motility[63]. The importance of CRF to these effects has been demonstrated using the non-selective CRF receptor antagonist, α-helical CRF[64]. Furthermore, the use of CRFR1 -/- mice has revealed the importance of the CRFR1 subtype in IBS like-symptoms, as these knock-out mice exhibit decreased visceral sensitivity[65], as well as decreased anxiety and an impaired stress response[66]. In addition CRF-evoked defecation in rats[67] is inhibited by blocking CRF1 receptors[68]. These results translate to IBS patients, where peripheral administration of CRF1 receptor antagonists reduces abdominal pain and anxiety[64]. In contrast to CRFR1-mediated increases in GI contractile activity, stimulation of CRFR2 is likely to result in inhibition of GI motility[69,70] and contribute to stress-induced colonic permeability dysfunction[71].

Effects of CRF on visceral hypersensitivity and colonic function

Some of the key symptoms of IBS, such as colonic motility, alterations in bowel habit and abdominal pain associated with gut hypersensitivity may be a consequence of CRFR1 signalling[72]. Consistent with this is increased thalamic expression of CRFR1 following colonic distension in the maternally separated rat model of IBS[73]. Moreover, central administration of CRF increases pain behaviours in response to colonic distension in rats[74] demonstrating the bidirectional signalling between the CNS and the gut. Activation of the CRFR1 signalling pathways causes increases in colonic motor activity and visceral pain[75,76], and conversely, activation of central and peripheral CRFR2 receptors delays gastric emptying[70]. Furthermore, activation of either CRFR1 or CRFR2 causes increased colonic permeability and inflammation[77]. The pathophysiology of stress-induced exacerbation of IBS symptoms may be due to central hypersecretion of CRF, as it has been shown that inhibition of CRFR1[78] as well as central inhibition with CRF antagonists decreases the response to water avoidance stress[79]. Also, stress increases intestinal permeability, visceral hypersensitivity, causes alterations in gastrointestinal motility and leads to profound activation of mast cells, resulting in the release of many pro-inflammatory mediators[80-82] which will be discussed in more detail later. Williams *et al*[67] illustrated that acute restraint stress increased large intestine transit rates and stimulated defecation and this was associated with mucosal mast cell activation[83,84], which was mediated by CRF[83]. These studies imply that the brain-gut axis of IBS patients has a magnified response to CRF. Thus, targeting CRF signalling molecules has been proposed as a potential treatment for IBS[70]. However, thus far, clinical trials using a CRFR1 antagonist have been disappointing[85].

Corticosteroids

Mineralocorticoids and glucocorticoids are steroid hormones which mediate the actions of the adrenal hormone, cortisol in the initiation and termination of the stress response, respectively[86]. Cortisol, which is the natural ligand for corticosteroid receptors, is elevated in IBS patients both at baseline and in response to stress[53,54]. In rodent studies, application of corticosterone to the amygdala induces colonic hypersensitivity and anxiety[87,88] and alters colonic transit[89], actions that are mediated through both mineralocorticoid and glucocorticoid receptors[90]. These studies demonstrate that central signalling by corticosteroids are potential targets for treating bowel dysfunction in IBS.

Glucagon-like peptide 1

A precipitating factor in symptom exacerbation is food ingestion, frequently in the form of abdominal pain and gas[91]. Although food intolerance has not been shown to cause IBS, ingestion of certain foods can result in abdominal pain, bloating, flatus and diarrhoea[92,93], especially carbohydrates, including gluten and lactose and fat-rich meals[92]. This appears to be more common in females and those who display increased anxiety levels again demonstrating the multi-factorial nature of IBS[93]. Prolonged and exaggerated colonic motor responses following a meal has been observed in IBS patients[94] and balloon distension in the jejunum demonstrated increased sensitivity in IBS patients following a meal[95]. Recent studies have reported the success of diets low in fermentable oligosaccharides, disaccharides, monosaccharides and polyols[96-98]. Reduction of poorly absorbed short-chain carbohydrates such as lactose, fructose and sorbitol, fructo-oligosaccharides, galacto-oligosaccharides and incompletely absorbed sugar polyols such as sorbitol and mannitol relieves symptoms of IBS, such as bloating, distension, abdominal pain, excessive flatus[98] and osmotic diarrhoea[99]. Although release of gas by fermentation is normal, the sensitivity of IBS bowels to distension results in visceral pain. The pathophysiological changes resulting in these symptoms are not yet clear. However, an important physiological response to the arrival of food in the GI tract is the secretion of incretin hormones such as glucagon-like peptide 1 (GLP-1) which is secreted by L-cells. The biological activities of GLP-1 include stimulation of glucose-dependent insulin secretion and insulin biosynthesis, inhibition of glucagon secretion and gastric emptying, and the inhibition of food intake. One report has related GLP-1 to IBS pathophysiology by demonstrating that a GLP-1 mimetic alleviated some of the pathophysiological symptoms of IBS with antispasmodic and pain-relieving properties[100]. Although, the molecular mechanisms by which GLP-1 achieves this outcome are not completely understood, it is thought to act in a neurocrine fashion. Indeed, GLP-1 has been found to increase firing rates in afferent vagal nerves[101]

and also decreasing neurally-evoked chloride secretion[102]. Interestingly, GLP-1 can also modulate GI secretion of cytokines and alter central CRF pathways that regulate stress-induced alterations in colonic transit[103]. GLP-1-expressing neurons are found in the enteric nervous system but also in brain regions such as the nucleus tractus solitarius and the ventrolateral medulla[104], revealing that the action of GLP-1 on gut function may be central or peripheral. GLP-1 activates the HPA axis through CRF neuronal stimulation, which may be important in the suppression of feeding behaviour[105]. Other GI hormones, such as motilin[106], which regulates the migrating motor complex in the fasting period and cholecystokinin[107] are elevated in IBS. In contrast, colonic expression of peptide YY[108] and circulating neuropeptide Y are lower in IBS patients[107]. Consideration must therefore be given to these and other GI factors in the pathogenesis of IBS.

ALTERATIONS IN IMMUNE FUNCTION IN IBS

Mounting evidence suggests that alterations in immune status such as elevations in mucosal mast cell numbers, pro-inflammatory cytokines and increased intestinal permeability are frequently noted in IBS patients[109]. Potential biomarkers of the disorder include alterations in cytokine profiles, mucosal and muscular infiltration of immune cells, changes in intestinal permeability and luminal microbiota which are discussed below.

Post-infectious IBS

Gross morphological evidence of inflammation is absent from IBS mucosal biopsies and other indicators of inflammation such as faecal levels of calprotectin and lactoferrin are not elevated[110,111]. Nonetheless, evidence is mounting on the important contribution of immune activation to the development of this syndrome. Indeed, one of clearest predictors of developing IBS is a prior history of bacterial or viral gastroenteritis[37,112], with one study showing a sevenfold increase in the risk of developing the functional bowel disorder following gastrointestinal infection[113]. Samples from individuals with post-infectious IBS show persistent increases in mucosal mononuclear immune cells[114], T-lymphocytes[115] and mast cells[116], which degranulate following stimulation releasing compounds such as histamine, tryptase and chymase. The extent of immune activation is an indicator of the severity of the infective gastroenteritis episode and the subsequent risk of developing IBS[114,117].

Immune cells and cytokines

Expression of lymphocytes and mast cells are elevated in IBS mucosal samples[118,119], although not all studies detected increased numbers of mucosal mast cells[118,120,121]. Nonetheless, soluble mediators released from degranulated mast cells were found to induce excitation of rat sensory neurons[121]. This has implications for GI sensory and motor function, with one study demonstrating that the colon is more susceptible to effects of stress on enteric nerve function following a prior bout of inflammation[122].

Evidence of immune activation in IBS includes elevated levels of pro-inflammatory cytokines such as interleukin (IL)-6 and IL-8[53,123-125], although not all studies detected such increases[120,126]. Furthermore, in peripheral blood mononuclear cells isolated from IBS patients, abnormal secretion of pro-inflammatory cytokines in response to immune challenges was observed[123,125,127]. Studies reporting changes in mucosal levels of pro-inflammatory cytokines in IBS biopsies varied with some studies describing an upregulation[116,128] but several others describing down-regulation of these cytokines[54,129]. That said, anti-inflammatory cytokines such as IL-10 and transforming growth factor β appear to be decreased in IBS colonic and rectal biopsies[54,128,129]. Expression of chemokines, including IL-8, CXCL-9 and monocyte chemoattractant protein-1, which are important in mucosal defence, were also decreased in IBS biopsies[129].

The source of these immune messengers are likely to be from mast cells, the numbers of which are elevated in IBS[128,130,131] and can secrete IL-6 and IL-1β[132] in addition to histamine, tryptase, chymase and proteases. Indeed, Buhner *et al*[131] described how excitation of non-IBS submucosal neurons with IBS biopsy secretions was dependent on serotonin, tryptase and histamine. Furthermore, the proximity of activated mast cells to colonic nerves was found to correlate with visceral pain severity[130].

Cytokines have been shown to have neuromodulatory effects with IL-6[133], IL-1β[134] and tumour necrosis factor (TNF) α[135] stimulating submucosal secretomotor neurons. This may result in changes in gut function including contractility[136], absorption and/or secretion[133]. IL-6 and IL-1β also influence mucosal ion transport and epithelial permeability and enhance cholinergically-mediated neurotransmission[133,137,138]. Furthermore, IL-6 has a potential role in neurogenic secretory diarrhoea[125] as this cytokine can suppress the inhibitory and anti-secretory effects of norepinephrine by blocking its release from sympathetic fibres[139]. Others have provided evidence that IL-6 attenuates the pre-synaptic inhibition of noradrenalin release, thereby releasing the sympathetic brake[134], which further contributes to a pro-secretory state. Aside from altered GI motility, the other main debilitating symptom of IBS is visceral pain sensitivity. Given the demonstrated effects of cytokines on enteric neuron excitability[133-135] and proven roles in nociception and sensory pain pathways[140], activation of enteric neurons and subsequent evocation of visceral pain make cytokines attractive candidates for mediating the visceral pain-related features of IBS.

Epithelial barrier integrity

The permeability of the epithelial layer which acts as a barrier between the external environment of the gut lumen and the body's internal milieu is an important consideration in immune activation in IBS. Indeed, some IBS patients have increased intestinal permeability[141], which

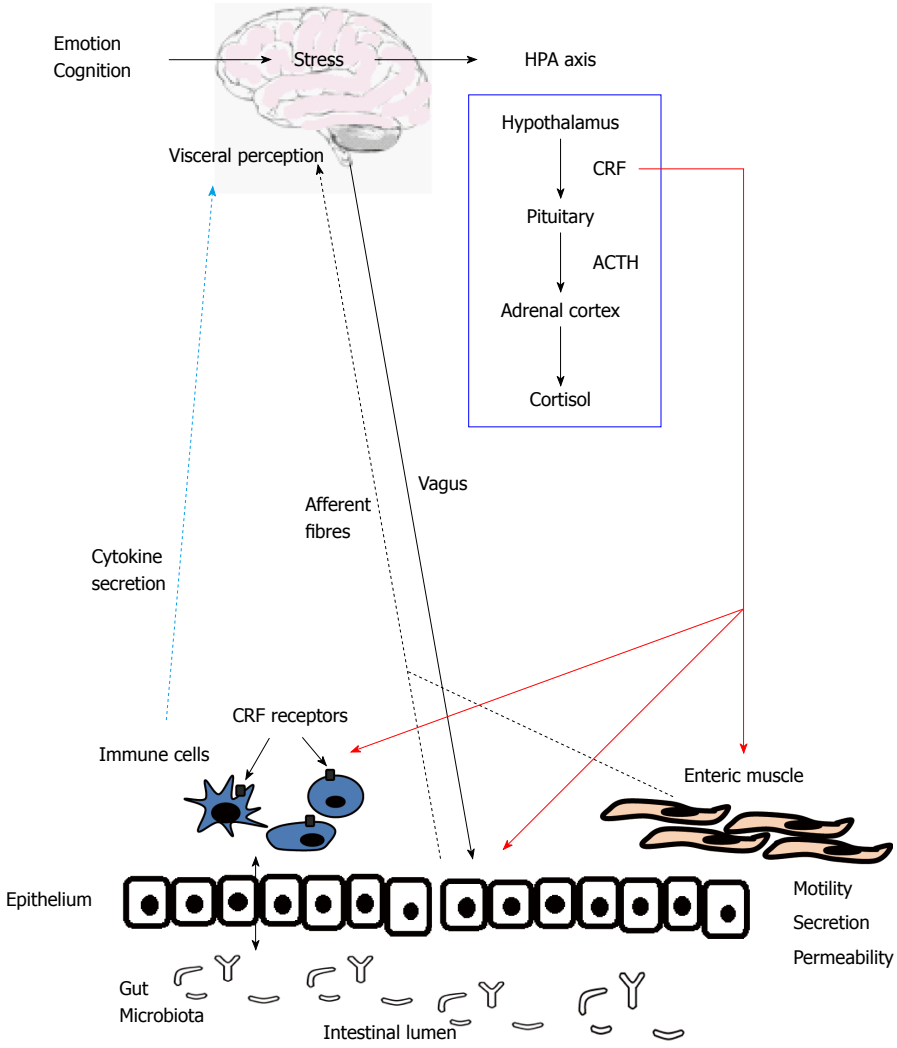

Figure 1 Convergence of neural endocrine and immune signalling pathways in bowel dysfunction. The figure illustrates the complex nature of functional bowel syndromes such as IBS. It illustrates interaction between three major bodily systems, neural pathways between the brain and gut, hormonal release, primarily from stress-induced activation of the HPA axis and secretion of immune factors such as cytokines. ACTH: Adrenocorticotropic hormone; CRF: Corticotropin-releasing factor; HPA: Hypothalamic-pituitary-adrenal; IBS: Irritable bowel syndrome.

may be due to proteasomal degradation of tight junction proteins[128,142]. Additionally, altered secretion of inflammatory cytokines may affect barrier function and permeability[129]. Breakdown of the mucosal barrier by IL-6 and other pro-inflammatory cytokines[137,143] may provide access for foreign proteins, thus initiating an immune response in the GI muscle layers resulting in changes in bowel function. In IBS, where circulating IL-6 levels are elevated and the HPA axis is hyper-activated[53], a coincident compromise of the mucosal barrier is observed. Thus, increased permeability of the mucosal barrier and the subsequent initiation of an immune response may contribute to the increase in sensitivity to visceral pain in IBS patients[144].

Microbiota

An additional factor contributing to brain-gut axis signalling in IBS currently gaining considerable attention is the importance of disrupting the luminal microbiota[145,146]. Indeed, microbiota dysbiosis, which may facilitate the adhesion of enteric pathogens in the human gut, has been reported in several IBS studies[147-150]. This virtual organ is integrated into the bi-directional communication in the brain-gut axis with studies demonstrating that microbiota dysbiosis exists in IBS patients and manipulation of the microbial environment with probiotics may lead to symptom improvement[151]. Probiotics have been shown to modulate the immune response in IBS, suppressing pro-inflammatory cytokines[152], maintaining intestinal barrier integrity[153], causing down-regulation of T cells and inhibition of nuclear factor kappa B[154]. Moreover, probiotics prevented adhesion of enteric pathogens to the wall of the GI tract[155]. However, more recent longer-term studies did not detect an improvement in symptoms[156,157]. Other members of the innate immune system that are altered in IBS include the pattern recognition receptors, toll-like receptors (TLRs), which recognise and respond to pathogens. Altered expression of TLR4, 5, 7 and 8 in mucosal biopsies from IBS patients further supports the importance of interactions between the luminal flora and

the host in this disorder[158].

CONVERGENCE OF PATHWAYS

The pathophysiology of altered bowel function in IBS patients remains unclear, however a number of mechanisms have been proposed to contribute to the initiation, exacerbation and persistence of symptoms. Alterations in brain-gut communication[159], stress[70], previous infections[57], abnormal microbiota[160], altered cytokine profiles[53] and increased intestinal permeability[142] have all been discussed. However, we believe that complex interactions between neural, endocrine and immune factors underlie the heterogeneity of symptoms that is characteristic of IBS as diagrammed in Figure 1.

For example, a perceived threat or stressor, which frequently precedes symptom flares, evokes responses from both the immune and stress systems. In healthy individuals this is a crucial response for the adaptation and ultimate survival of an organism. However, in the case of PI-IBS, co-morbidity with anxiety or depression and the occurrence of stressful life events around the time of exposure to the enteric pathogen have been independent predictors of risk for the development of IBS[114,161,162], although not all studies, including the Walkerton cohort[112], detected this association. IBS patients are more likely to be stress-sensitive, as measured by the Holmes and Rahe stress scale, and exhibit elevated numbers of colonic mucosal mast cells[130]. Moreover, acute stress causes increases in the numbers of white blood cells, natural killer cells and CD8+ T-lymphocytes, decreases B cell numbers and stimulates secretion of pro-inflammatory cytokines[163,164], whereas secretion of glucocorticoids and an associated decrease in secretion of pro-inflammatory cytokines is noted in cases of chronic stress[165]. Patients with IBS often exhibit concurrent increases in markers of a hyperactive stress response and immune upregulation such as CRF-stimulated HPA axis hyper-responsivity which is related to the elevation in IL-6 levels[53]. CRF also stimulates the recruitment and activation of granulocytes[166] and mast cells[167] to the gut mucosa.

Immune cells express receptors for several different stress-related peptides including CRF[168]. Indeed, we have detected both CRFR1 and IL-6 receptors on T-helper cells[169]. CRF peptides have potent immunomodulatory actions[170], including degranulation of mast cells[171] and secretion of cytokines[53,172], although it is not yet clear whether these effects are pro-[173] or anti-inflammatory[174,175].

In terms of crosstalk between the stress system and the neural response, many of the psychological disorders frequently found to be co-morbid with IBS also have the capacity to disrupt autonomic balance[52] and indeed, anxiety and depression are associated with depressed parasympathetic activity in IBS patients. Enteric neurons, which directly regulate absorpto-secretory function and gut motility have been shown to express both CRF receptors and IL-6 receptors[169]. Indeed, cytokines such as IL-6 can directly induce excitation of enteric neurons in animal models of IBS[133,176]. IL-6[133], IL-1β[134] and TNFα[135] can cause activation of submucosal secretomotor neurons thereby acting as neuromodulatory factors that can directly influence such gut functions as motility, absorption, secretion and blood flow. IL-6 and IL-1β also have effects on mucosal ion transport and epithelial permeability, in addition to enhancing cholinergically-mediated neurotransmission[133,137,138]. Indeed, soluble mediators released from mast cells in IBS biopsies were found to have excitatory effects on rat sensory neurons[121].

Although the pathophysiology of IBS still requires further elucidation, recent progress in the field has demonstrated the importance of molecular factors such as the stress hormone, CRF and cytokine release and their influence on neural communication between the brain and gut. Further research will hopefully reveal the aberrant signalling between endocrine, immune and neural systems in IBS patients and pave the way towards effective new therapies for this common bowel disorder.

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