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Latest Insights on the Pathogenesis of Irritable Bowel Syndrome

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Latest insights on the pathogenesis of IBS

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Abstract

The pathogenesis of irritable bowel syndrome (IBS) is multifactorial and complex. Our understanding of IBS pathophysiology has evolved over the years but is still not completely understood. However, a unifying theme is that the symptoms of IBS result from a dysregulation of brain–gut interactions, which clinically presents as enhanced visceral perception and altered bowel habits. Scientific evidence has identified alterations in central and peripheral (gut) mechanisms in IBS and the bidirectional communication between the brain and the gut. Pertinent mechanisms linked to IBS include a gut motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing. This review addresses the factors that increase the risk of IBS and the central and peripheral mechanisms thought to underlie the symptoms of IBS.

Key words: irritable bowel syndrome, IBS, pathogenesis, stress, genetics, visceral hypersensitivity

Key Points:

- Irritable bowel syndrome (IBS) is considered a disorder of gut brain interaction (DGBI) that is classified by GI symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing.
- Symptoms of IBS result from dysregulation of brain–gut interactions, which manifests as enhanced visceral perception and altered bowel habits.
- Factors that increase the risk of developing IBS include genetic and environmental factors (e.g. early adverse life events) and infection. Factors which trigger symptoms in patients with IBS include food and stress.
- Patients with IBS have enhanced visceral perception due to peripheral and/or central sensitization.
- Peripheral pathophysiologic mechanisms in IBS include alterations in neuronal function, luminal and tissue mediators, immune response, intestinal permeability, bile acid processing, serotonin signaling, and gut microbiota.

Introduction

The pathogenesis of irritable bowel syndrome (IBS) is complex, and while it has evolved over the years (**Figure 1**), it is still not well understood. A unifying theme is that the symptoms of IBS result from dysregulation of brain–gut interactions, which manifests as enhanced visceral perception and altered bowel habits. Growing scientific evidence has led experts to redefine IBS and other functional gastrointestinal (GI) disorders to disorders of gut brain interaction (DGBI) which is classified by GI symptoms related to any combination of the following: motility disturbance, visceral hypersensitivity, altered mucosal and immune function, altered gut microbiota, and altered central nervous system (CNS) processing.[1] There are factors that increase the risk of developing IBS and include genetic predisposition, environmental factors (e.g. early adverse life events), and infectious gastroenteritis. Other factors trigger symptoms once IBS manifests and these include food and stress (**Figure 2**). Thus, IBS may represent a combination of factors involving different pathophysiologic mechanisms. Given the complex pathophysiology of IBS, there is currently no single biomarker that can represent the different pathophysiological mechanisms of IBS.

Factors that increase the risk of IBS

Familial and genetic factors

Studies have demonstrated that IBS clusters in families.[2] A case–control study studied 477 IBS patients and 1492 of their first-degree relatives and 297 controls and 936 of their first-degree relatives. There was a higher proportion of IBS relatives with IBS compared

to control relatives (50% vs. 27%; OR of 2.75 [95% CI 2.01– 3.76]).[3] Another large study employed the Swedish Multigeneration Register which included 60,489 sibling pairs and found an OR of 1.75 (95% CI 1.63 to 1.89) for IBS in full siblings.[4]

Most, but not all, twin studies suggest heritability of IBS,[2] although there also appears to be a strong environmental influence. For example, one twin study found that the concordance of having IBS was higher among monozygotic twins than dizygotic twins but showed that the presence of IBS in the mother was also a strong predictor of having IBS.[5] The role of environmental influences on IBS is further supported by the Swedish Multigeneration Register study which found that the OR for spouses having IBS was 1.51 (95% CI 1.24 to 1.84).[4] These findings suggest that environmental factors, including learned behavior, can contribute to the development of IBS symptoms.

In addition to familial clustering and twin studies in IBS,[4, 6] genetic association studies support that there is genetic predisposition to developing IBS. The first large genome-wide association study (GWAS) in IBS consisted of 534 IBS patients and 4932 controls without recurrent abdominal problems.[7] No single nucleotide polymorphisms (SNPs) met the significance threshold for genome-wide association ($p < 5 \times 10^{-8}$). However, there were 14 genes with a $p < 10^{-4}$ that selected for validation in several population-based case-control cohorts (n = 3,511). One locus (7p22.1) was found to be significant and includes the genes KDEL endoplasmic reticulum protein retention receptor 2 (*KDELR2*) and glutamate receptor, ionotropic, delta 2 (Grid2) interacting protein (*GRID2IP*).[7]

A subsequent, larger GWAS study used a population-based cohort in the United Kingdom that included 9,576 cases with self-reported IBS and 336,499 controls.[8] One

locus, rs10512344 on chromosome 9q31.2, was significantly different in IBS and controls. This finding was also replicated in a multi-national cohort of 2045 IBS and 7955 controls. Interestingly, the 9q31.2 SNP was entirely accounted for by the female group and had strongest genetic risk effects in age at menarche. Age at menarche is thought to be an indicator of possible health complications and disease later life. This study also found that IBS risk genes were enriched for intracellular calcium activated chloride channel activity, ion gated channel activity, and anion channel activity, and for targets of the miR-15 family of microRNAs.[8]

Other genetic studies found that 2-3% of IBS patients have rare functional variants of the voltage-gated channel $Na_v1.5$ (*SCN5A*) causing a channelopathy or the sucrose isomaltase (*SI*) gene causing carbohydrate malabsorption.[9, 10]

There are multiple studies that have evaluated the association of the serotonin transporter gene, known as 5-HTTLPR, with IBS. While high quality studies and a meta-analysis failed to find a significant association of 5-HTTLPR with IBS,[11, 12] several other studies did find an association.[13, 14] In one study, a higher colonic mucosal expression of SERT mRNA and protein was seen for the L/L genotype of this SNP, which was more common in constipation-predominant IBS (IBS-C).[13] Other SNPs that have been associated with IBS are found in the genes for corticotropin releasing factor receptor 1 (CRF-1R),[15] catechol-O-methyltransferase (COMT), interleukins and TNF-α.[6, 14]

In addition to genetic risk factors, researchers have identified alterations in a variety of epigenetic factors in IBS which were recently reviewed (**Figure 3**). [16] Epigenetics

refers to modifications in gene expression that can change the phenotype without changing genetic sequence (genotype). Epigenetic changes described in IBS include alterations in gene methylation[17] and expression of non-coding microRNAs.[16] These epigenetic changes may be due, at least in part, to early adverse life events (EALs), e.g. abuse, which are increased in IBS patients compared to healthy controls (see below).[18, 19] Animal[20] and human[21, 22] studies have demonstrated that EALs are associated with epigenetic modifications, which can result in long-term effects. Future studies are needed to validate some of these genetic and epigenetic findings and to determine their functional relevance in IBS.

Prior gastrointestinal infection

Post-infection IBS (PI-IBS) is the new onset of IBS symptoms following resolution of an acute infectious gastroenteritis. Acute gastroenteritis is characterized by two or more of the following: fever, vomiting, diarrhea, or a positive bacterial stool culture.[23] GI infection is the strongest risk factor for IBS and increases the risk of IBS at 12 months by about 4-fold.[24] Individuals who are particularly at risk for PI-IBS are those with a history of gastroesophageal reflux disease (GERD) or dyspepsia, more severe diarrheal illness, younger age, female gender, anxiety or depression, or chronic stressful life events at the time of the infection.[23] The bowel habit subtypes most often seen in PI-IBS are diarrhea or mixed bowel habit [23]. With regard to type of pathogen causing PI-IBS, pooled incidence rates were: bacterial, 13.8%, protozoal/parasitic, 41.9%, and viral, 6.4%.[24]. The highest incidence of PI-IBS was 35-45% which occurred with a drinking water outbreak with both *Campylobacter jejuni* and *Escherichia coli* O157 : H7.[25]

Stressful life events

Studies have demonstrated an association between current stressful life events in childhood and/or adulthood and IBS.[18, 19] The association of stress and IBS is further supported by the finding that stressful life events increased the risk of developing PI-IBS.[26] IBS patients have a higher prevalence of early adverse life events (EALs) during childhood that include physical, sexual or emotional abuse, severe illness or death of a parent, incarcerated individual in the household, perinatal gastric suctioning, and exposure to wartime conditions.[27-31]

In a recently published study, we found that stressful life events experienced in adulthood is also associated with IBS.[19, 32] IBS patients perceive life events as more negative than healthy controls. The presence of more-negatively perceived adulthood life events was associated with worse IBS symptom severity and poorer IBS-related quality of life. Negatively perceived adulthood life events were also associated with a dysregulated stress response to hormone challenge in patients with IBS compared with controls.

Deployment during wartime is a significant stressor associated with IBS. IBS has been recognized as a part of the "Gulf War Syndrome." In a study of US Navy Seabees, who are known to be among the most symptomatic Gulf War veterans, those who were deployed to the Persian Gulf were over three times more likely to have IBS compared to Seabees deployed to other locations or not deployed.[33] Another study found that Persian Gulf veterans with chronic GI symptoms showed evidence of visceral and somatic hypersensitivity.[34] It would be helpful to know if these individuals developed

new-onset symptoms after deployment or if their symptoms were present pre-deployment and were exacerbated by wartime stress.

It is important to understand the stressors that trigger the onset and exacerbations of IBS symptoms to help guide disease management.

Pathophysiologic mechanisms of IBS

Increased visceral perception

Gut sensation and function is influenced by activity of the gut lumen, mucosa and submucosa, enteric nervous system (ENS), and central nervous system (CNS), and the communication between these entities (**Figure 4**). Stimuli within the gut, e.g. mechanical or chemical stimuli, are detected by primary afferent nerves, which are extrinsic, intrinsic, or intestinofugal. Spinal afferent nerves project to the dorsal horn of the spinal cord with cells bodies located in the dorsal root ganglia. The sensory input ascends along the dorsal column and then to the contralateral ventroposterolateral nucleus of the thalamus and to various cortical regions. Brain networks, including the sensorimotor, salience, central autonomic, emotional arousal and central executive neworks, process and modulate visceral input.[35] Under normal circumstances, visceral signals are evaluated by the salience network and insula which assesses the importance of these signals and whether they are perceived as normal gut sensations, discomfort or pain. Brain outputs include autonomic nervous system responses, which regulate gut and immune function, and

descending pain modulatory pathways, which regulate pain sensitivity at the dorsal horn level of the spinal cord.

Increased perception of visceral stimuli and IBS symptoms develops from either greater sensitivity of visceral afferent pathways (peripheral sensitization) or central amplification of visceral afferent input at the brain and spinal cord level (central sensitization).[35] Peripheral sensitization of sensory nerves occurs when nerves are activated by mediators released from immune cells and epithelial cells, or via alterations in second messenger systems or gene expression.[35] Increased visceral stimulation, e.g. due to injury or inflammation, can lead to increased CNS responsiveness, or central sensitization, which results in decreased sensory thresholds (i.e, increased sensitivity).

Enhanced visceral perception as measured by increased perception to a rectal or colonic balloon distension has been demonstrated in a significant subset of patients with IBS by multiple research centers.[36-38] IBS patients demonstrate decreased pressure thresholds to pain and discomfort, and/or increased perceptual ratings and viscerosomatic referral areas to balloon distension in the intestine. The fact that enhanced visceral perception is not present in all IBS patients and that sensory thresholds only modestly correlate with symptoms limits sensory thresholds to distension as a diagnostic and therapeutic biomarker.[36, 37]

Altered CNS processing and modulation

Brain imaging studies have demonstrated both structural and functional alterations in task-related brain networks in patients with IBS compared to healthy controls with some of the findings correlating with IBS symptom severity.[35, 39] In addition, studies

suggest that emotional factors can influence visceral perception and contribute to the differences between IBS patients and healthy controls.[40] A comprehensive review on the role of brain imaging in IBS and other DGBI summarized the alterations in the functional, structural and anatomical networks in the resting state and in response to task related functions reported in these conditions. These networks include the default mode, emotional arousal, central autonomic control, central executive control, sensorimotor processing and salience. Neuroimaging findings in IBS patients include: 1) greater cortical thickness and volume of sensorimotor cortex that correlates with symptom severity, particularly in women, 2) alterations in functional connectivity of anterior insula and amygdala, 3) greater engagement of the salience detection and emotional arousal networks in response to actual and expected rectal distension, 4) decreased corticolimbic inhibitory feedback, and 5) increased activation of central autonomic network that regulates autonomic nervous system response.[41] Alterations in these networks provide conceivable explanations for increased anticipatory anxiety and hyperattentiveness to GI sensations, catastrophizing behavior, autonomic hyperarousal, and expectancy of outcomes in IBS.[41]

GI transit and motility

Multiple studies have reported alterations in small intestinal and colonic motility in IBS. Findings in IBS include increased motility in fasting states and in response to meals and cholecystokinin,[42] increased number of rapid contractions in response to balloon distention, [43] accelerated transit time in a subset of diarrhea-predominant IBS (IBS-D) [44], and that changes in motility can be induced by psychological and physical stress.

[45] While transit differs between bowel habit subtypes, abnormal transit is more likely to be present in patients with IBS-D (accelerated in up to 48%), and less so in patients with IBS with constipation (IBS-C) (delayed in 21%).[46]

Peripheral factors involved in IBS pathogenesis

The interplay of multiple luminal and peripheral factors can contribute to changes in GI function and ultimately symptoms of IBS (**Figure 5**). In the gut, the network of multiple cells including epithelial, immune, neuronal, microbiota comprise the "gut connectome" which communicates with the brain via neural, endocrine and inflammatory pathways. The brain to gut communication is mainly mediated via the autonomic nervous system pathways to the gut.[41]

Nerve fibers. An increase in nerve fibers, e.g. those expressing receptors for substance P and transient receptor potential vanilloid type 1 (TRPV-1), cannabinoid receptors,[47] and protease-activated receptors (PAR)[48] are present in IBS patients compared to controls.[49]. Further support of the significance of neuronal mechanisms in IBS is demonstrated by a study where colonic mucosal gene expression profiling was conducted in patients with IBS-C and IBS-D and healthy controls and compared to publicly available profiling data from additional cohorts.[50] Gene profiling and network analyses revealed pathways and genes related to neurally-mediated pain in IBS, particularly IBS-C.

Luminal and tissue mediators. Several studies have demonstrated that luminal or tissue mediators can sensitize primary afferent nerves and contribute to increased visceral sensitivity in IBS. Supernatants from mucosal biopsies from IBS patients increase firing of afferent neurons in animal models[51, 52] and submucosal neurons in human biopsies.[53] A class of mediators that is thought to increase neuronal activity is proteases which are increased in IBS supernatants. Furthermore, protease inhibitors decrease the heightened visceral sensitivity that occurs from intracolonic administration of IBS biopsy supernatants in mice.[51] Histamine is another mediator that has been shown to increase excitation of TRPV1 neurons via the histamine 1 receptor.[54]

Altered mucosal barrier function. Based on different methods of measuring intestinal permeability, there is evidence that a subset of IBS patients (particularly PI-IBS and IBS-D) have increased intestinal permeability. There is decreased expression of tight junction proteins in the colon and jejunum of patients with IBS-D.[55] Increased permeability has been associated with greater abdominal pain severity and visceral hyperalgesia.[56, 57]. Alterations in mucosal barrier function appears to play a role in the interaction between stress, visceral hypersensitivity, and altered immune function and gut microbiota in IBS. Intestinal permeability has also become a therapeutic target for IBS treatments.

Altered immune function. Increased immune activation is thought to play a role in the pathophysiology of IBS. This is best demonstrated in PI-IBS, where increased numbers of T lymphocytes and levels of pro-inflammatory cytokine interleukin-1β (IL-1β) in the rectal mucosa were present compared to that in controls.[26, 58] Interestingly, sensitization of TRPV1 neurons persisted two years following the gastroenteritis but

differences in lymphocytes or mucosal cytokine mRNA expression were no longer present.[59] These findings suggest that immune changes may be transient and could explain the inconsistent and conflicting results in unselected IBS patients.

A systematic review and meta-analysis of 22 studies found increased mast cells and CD3+ cells in the left colonic mucosa in IBS patients compared to controls.[60] There has been much interest in the role of mast cells in increasing peripheral sensitization and intestinal permeability in IBS through release of histamine.[49, 61] One study demonstrated an increased number of mast cells in close proximity to sensory neurons in IBS patients compared to controls and this correlated with increased abdominal pain severity and frequency.[61] Increased mast cells have also been associated with increased colonic permeability and diarrhea symptoms.[62] However, other studies have found comparable or even lower numbers of mucosal immune cells in IBS and controls.[51, 63, 64]

There have been studies showing increased pro-inflammatory cytokine and/or lower anti-inflammatory cytokine profiles in IBS patients, but this has been mainly in blood samples and not in the colonic mucosa.[65] Increased tumor necrosis factor alpha (TNF-α) and and interleukin 6 (IL-6) levels were present in IBS compared to controls,[66, 67] although other studies contradict these findings.[63, 68] Furthermore, SNPs in genes encoding proinflammatory cytokines such as IL-6 and the anti-inflammatory cytokine interleukin 10 (IL-10) were associated with IBS.[69, 70] Colonic mucosal cytokine levels are more variable, however a few studies have shown decreased levels of the anti-inflammatory cytokine, IL-10.[63, 71] Most studies have failed to show a significant association between cytokine levels or cell counts with symptoms.[63, 66-68]

Bile acid processing. Bile acid diarrhea is reportedly present in around 25% of IBS with diarrhea patients.[72-74] Bile acids increase secretion, motility, and visceral sensitivity to rectal distention. Bile acid-related visceral hypersensitivity is thought to be due to activation of the farnesoid X receptor (FXR) on mast cells resulting in increased expression of nerve growth factor and subsequent increased TRPV1 expression on dorsal root ganglion neurons.[75] Bile acids may also be clinically relevant in some patients with IBS-C who have reduced total bile acids and reduced fecal deoxycholic acid.[76, 77]

Serotonin signaling mechanisms. About 95% of serotonin (5-HT) is present in the GI tract. It is stored in enterochromaffin cells (ECCs) and in enteric serotonergic neurons. [78] ECCs release 5-HT in response to a variety of stimuli. Serotonin is a neurotransmitter and binds to receptors on enteric neurons and vagal and spinal afferent nerves, which modulate gut motility, secretion, and sensation. Serotonin is taken up into cells via a reuptake transporter proteins, such as the serotonin reuptake transporter, SERT. Gut microbiota and their metabolites, including short-chain fatty acids (SCFAs) and secondary bile acids, can influence 5-HT signaling and GI function including by activation of intrinsic and extrinsic GI nerve reflexes.[79, 80]

A number of studies support that serotonin is involved in the altered motility and transit present in IBS patients. Postprandial platelet depleted plasma 5-HT levels are elevated in IBS-D patients and correlate with more rapid colonic transit times.[81, 82] In IBS-C patients, serotonin is thought to have impaired release since ECCs have increased serotonin content but postprandial 5-HT levels are low.[81] The significant role of

serotonin in IBS is supported by the efficacy of several approved serotonergic agents in the treatment of IBS.

Gut microbiota. There is growing evidence that gut microbiota may play a role in IBS. However, studies comparing the fecal microbiome in IBS patients and healthy controls have variable findings. A recent meta-analysis of 24 studies found that microbial diversity was reduced in IBS and that the microbiome of IBS patients had increased abundance of family Enterobacteriaceae, family Lactobacillaceae, and genus Bacteroides, and decreased abundance of Clostridiales I, genus Faecalibacterium, and genus Bifidobacterium.[83] Microbiota have been associated with gut motility and transit in animal models. It is thought that these effects relate to neuroactive microbial metabolites, but direct evidence supporting this hypothesis is lacking.[84, 85]

Microbes also contribute to the bidirectional communication within the brain-gut axis. The brain receives complex afferent input from the gut and microbial metabolites, and in turn sends modulatory signals back to the gut primarily via the autonomic nervous system, which in turn influence intestinal and gut microbial function. Altered gut microbial metabolites can also feed back to the brain, influencing pontine arousal systems and brain networks.[84]

Dysregulated stress responsiveness

IBS is considered a stress-sensitive disorder. The stress response is an integrated and coordinated physiological process that can result in physiological adaptation or pathological maladaptation. The main central stress response output systems are the hypothalamic-pituitary-adrenal (HPA) axis and the locus coeruleus-noradrenergic system.

Stress is perceived or actual perturbation in homeostasis.[86] “Allostasis” refers to the active process of adapting to stressors via mediators such as cortisol and the autonomic, metabolic and immune system that act together to maintain homeostasis. Chronic wear and tear on the body can lead to disease or reaching one’s “allostatic load or overload” which

refers to the cumulative effect of multiple stressors as well as the dysregulation of allostasis (eg. too much or too little cortisol, or adrenalin or inflammation in response to a challenge).

The allostatic load results from either too much stress or not efficiently responding to the stress.[86]

Activation of the HPA axis results in synthesis and release of corticotropin releasing factor (CRF) in the paraventricular nucleus of the hypothalamus. CRF stimulates release of adrenocorticotropin hormone (ACTH) from the anterior pituitary gland, which leads to the release of cortisol from the adrenal glands. Cortisol levels are regulated by negative feedback at the level of the hypothalamus and the pituitary. CRF also acts as a neurotransmitter and activates the autonomic nervous system, resulting in an integrated response to stress.

Experimental stress increases visceral sensitivity, gut motility and permeability, and immune response (**Figure 6**).[38, 87, 88] The HPA axis has also been associated with visceral sensitivity via central sensitization at the level of the dorsal root ganglia and brain.[89, 90] Altered HPA axis responses have been demonstrated in IBS patients compared to controls.[91] These alterations have been shown to be associated with an

increased number of early adverse life events, negatively perceived stressful life events in adulthood and reduced resilience which have all been demonstrated in IBS.[19, 32, 92, 93] Enhanced HPA axis response in early life stress models has been linked to decreased negative feedback due to increased DNA methylation of the glucocorticoid receptor promoter which results in decreased glucocorticoid receptor expression.[20]

IBS patients show changes in autonomic nervous system tone, specifically a greater sympathetic/parasympathetic (vagal) balance[94] with differences occurring between bowel habit subtypes [95] and men and women.[96, 97] Autonomic nervous system changes are also seen in patients with more severe symptoms. The autonomic nervous system's effect on pain sensitivity, immune response and gut motility are particularly relevant in the pathogenesis of IBS.

Summary

Valuable scientific advances have been made over the past few decades which have improved our understanding of the pathogenesis of IBS. While there is not a consensus on the exact, underlying mechanisms to explain the symptoms of IBS, this condition is now well recognized as a disorder of gut-brain interactions. Evidence suggests that although IBS is characterized by the presence of abdominal pain associated with altered bowel habits, it remains a heterogenous disorder where the cluster of IBS symptoms may arise from several etiologies that can differ within subgroups of patients. IBS symptoms can arise from various primary peripheral or central mechanisms, but once brain–gut interactions become altered, it is more challenging to identify causality.[35] Future efforts to integrate multiple levels of data (e.g., symptoms, gene and protein expression,

neuroimaging measures, microbial-related measures) to identify phenotypic subgroups with specific pathophysiologic mechanisms that may serve as diagnostic and/or therapeutic targets are needed.

Figure legends

Figure 1. History of physiological research in IBS and FGIDs. This timeline shows some of the key research studies on the top and the domains of research on the bottom. From 1950 up until 1990 research was primarily that of motility, however after 1990 there began new research in the areas of visceral hypersensitivity, brain gut interactions, inflammation, the microflora, and food and diet. It was the Rome classification system and criteria that allowed for identification of patients with disorders of gut-brain interaction for research in these other domains. Permission obtained from the Rome Foundation.

Figure 2. Proposed Pathophysiologic Model of IBS. There are factors that increase risk of developing IBS which include genetic factors, environmental factors such as early adverse life events, e.g. abuse, and infection. The alterations in brain-gut interactions result in multiple central and peripheral mediated pathophysiologic mechanisms (shown in blue box). Once the symptoms of IBS occur, there can be triggers that increase symptom severity, such as food and stressors. The symptom burden and coping behaviors will influence health care seeking. Permission obtained from the Rome Foundation.

Figure 3. Schematic model of genetic and epigenetic factors influencing IBS. Pink arrows illustrate that genetic factors including SNPs can influence the gene expression either directly or mediated by epigenetic factors including DNA methylation, histone modifications, miRNA and lncRNA expression (purple arrow).
Environmental factors including stress and psychological factors at the central nervous system (CNS) level and dietary factors at gastrointestinal level can induce changes in gene expressionmediated by epigenetic or non-genetic/epigenetic factors, and can have a direct influence on CNS and gut function (blue arrows). Peripheral or gut factors including GI infection or other host or microbial factors, can potentially modify the function of genes mediated by epigenetic or non-epigenetic factors, and influence the CNS and gut function (green arrows) such as, pain modulation, sensation, immunity, barrier function, colonic transit and secretion to manifest the symptoms of IBS (orange-red arrow). From Mahurkar-Joshi S, Chang L. Epigenetic Mechanisms in Irritable Bowel Syndrome. Front Psychiatry. 2020 Aug 14;11:805. doi: 10.3389/fpsyt.2020.00805.

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Figure 4. Integrated brain–gut model of IBS pathophysiology. This figure is a proposed model for involvement of brain–gut axis in the generation of IBS symptoms (chronic abdominal pain associated with altered bowel habits). Under normal circumstances, visceral and external signals are evaluated by the salience network, which

generates brain outputs in terms of targeted ANS responses (regulating gastrointestinal and immune function) and descending pain modulatory activity (regulating pain sensitivity at the dorsal horn level). Target organ alterations (either peripherally or ANS stimulated) are signalled back to the brain via neural, endocrine or immune-related channels. These signals are processed within subregions of the INS, and depending on their subjective salience, are consciously perceived (associated with activation of anterior INS) as normal gut sensations, discomfort or pain. IBS symptoms can arise from several primary peripheral or central mechanisms. Abbreviations: Amyg, amygdala; ANS, autonomic nervous system; dACC, dorsal anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; Hypo, hypothalamus; INS, insula; orbFC, orbitofrontal cortex; PAG, periaqueductal grey; rACC, rostral anterior cingulate cortex; RVM, rostral ventromedial medulla. Figure from Mayer EA, Labus JS, Tillisch K, Cole SW, Baldi P. Towards a systems view of IBS. Nat Rev Gastroenterol Hepatol. 2015 Oct;12(10):592-605. doi: 10.1038/nrgastro.2015.121. Epub 2015 Aug 25.
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Figure 5. Cross-talk at the mucosal border. Cellular and molecular factors involved in epithelial barrier alterations in irritable bowel syndrome patients. Mucosal immune cells including B cells, T cells, other local cells such as enteroendocrine (EC) cell and mast cells (MC) can release several soluble mediators to alter tight junction (TJ) function, thus increasing paracellular permeability. In the lumen of the gut, bacterial products including serine and cysteine proteases and bile salts are able to increase paracellular permeability. These epithelial barrier defects allow the perpetuation of a mucosal low-grade immune activation associated with the stimulation of afferent nerves fibers. Figure modified from Piche T. Tight junctions and IBS--the link between epithelial permeability, low-grade inflammation, and symptom generation? Neurogastroenterol Motil. 2014 Mar;26(3):296-302. doi: 10.1111/nmo.12315. PMID: 24548256. Permission obtained from the Rome Foundation.

Figure 6. Stress-Induced Physiologic Changes in IBS. Experimental stress has been shown to be associated with physiologic changes involved in brain-gut interactions and are relevant in IBS pathogenesis. Stress can alter gastrointestinal motility, intestinal permeability and secretion, the hypothalamic-pituitary-adrenal axis, visceral perception thresholds and ratings to balloon distention of the rectum and colon, and autonomic nervous system tone. Abbreviations: GI, gastrointestinal; HPA, hypothalamic-pituitary-adrenal, IBS, irritable bowel syndrome. Data from 1. Chang L. Invited review: The role of stress on physiologic responses and clinical symptoms in IBS. Gastroenterology 2011;140(3):761-765 and 2. Vanuytsel T, van Wanrooy S, Vanheel H, Vanormelingen C, Verschueren S, Houben E, Salim Rasoel S, Tóth J, Holvoet L, Farré R, Van Oudenhove L, Boeckxstaens G, Verbeke K, Tack J. Psychological stress and corticotropin-releasing hormone increase intestinal permeability in humans by a mast cell-dependent mechanism. Gut. 2014 Aug;63(8):1293-9.

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