RESEARCH PAPER

Gut–Brain Axis Dysregulation in Irritable Bowel Syndrome: From Stress Signaling to Therapeutic Opportunities

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Abstract
Irritable bowel syndrome (IBS) is a chronic disorder of gut–brain interaction characterized by recurrent abdominal pain associated with altered bowel habits. Its pathophysiology is multifactorial and involves disturbances in gastrointestinal motility, visceral sensation, intestinal barrier function, gut microbiota, mucosal immunity, neuroendocrine signaling, and central pain processing. Increasing evidence indicates that communication between the gastrointestinal tract and the central nervous system through the gut–brain axis (GBA) has a central role in the development and persistence of IBS symptoms. Psychological stress can activate the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system, resulting in alterations in gastrointestinal motility, epithelial permeability, immune activity, microbial composition, and visceral sensitivity. Conversely, intestinal microbial metabolites, immune mediators, and neural signals can influence central stress and pain pathways, establishing a bidirectional feedback system. Dysbiosis, intestinal barrier dysfunction, mast-cell activation, neuroimmune signaling, and visceral hypersensitivity may therefore act as interconnected mechanisms rather than isolated abnormalities. Current management includes dietary modification, pharmacological treatment, microbiota-directed interventions, and gut-directed psychological therapies. Emerging strategies targeting microbial metabolites, mast-cell signaling, vagal pathways, and neuromodulation may provide additional therapeutic opportunities. This review discusses the mechanisms linking stress and GBA dysregulation with IBS and examines established and emerging therapeutic approaches, with emphasis on the potential for mechanism-based and individualized management.

Keywords: Irritable bowel syndrome; gut–brain axis; disorders of gut–brain interaction; psychological stress; HPA axis; gut microbiota; intestinal barrier; visceral hypersensitivity; neuroimmune signaling; neuromodulation.
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1. Introduction

Irritable bowel syndrome is one of the most common disorders of gut–brain interaction (DGBI). It is characterized primarily by recurrent abdominal pain associated with defecation or changes in stool frequency or form. IBS is generally categorized into IBS with constipation (IBS-C), IBS with diarrhea (IBS-D), IBS with mixed bowel habits (IBS-M), and IBS that does not meet the criteria for these subtypes. The Rome IV framework shifted the conceptualization of these conditions from traditionally defined functional gastrointestinal disorders toward DGBI, emphasizing the importance of bidirectional communication between gastrointestinal and central nervous system processes [1].

IBS has a substantial population burden, although reported prevalence varies considerably according to diagnostic criteria, geographical region, sampling methodology, and study population. A recent systematic review and meta-analysis found higher estimated prevalence when Rome IV criteria were used compared with earlier Rome criteria, illustrating how diagnostic definitions influence epidemiological estimates [2].

The pathophysiology of IBS is heterogeneous. Altered intestinal motility, visceral hypersensitivity, epithelial barrier dysfunction, mucosal immune activation, changes in the gut microbiota, altered autonomic regulation, and abnormal central pain processing have all been implicated. These mechanisms interact with psychological and environmental factors rather than acting independently [3].

The GBA provides an integrated framework for understanding these interactions. It comprises the central and enteric nervous systems, autonomic pathways, vagal and spinal afferents, endocrine signaling, immune mechanisms, intestinal epithelial

barrier, and gut microbiota. Disruption of communication within this network may contribute to symptom generation and persistence in IBS.

2. Gut–Brain Axis and IBS

The GBA is a bidirectional communication network connecting the brain and gastrointestinal tract through neural, endocrine, immune, and microbial pathways. The enteric nervous system (ENS) regulates gastrointestinal motility, secretion, and local reflexes, whereas the autonomic nervous system (ANS) provides major communication pathways between the gut and brain.

The vagus nerve is an important component of this system because it carries visceral sensory information to the brain and provides efferent regulation of gastrointestinal functions. Through these pathways, alterations in gastrointestinal activity can influence central physiological and emotional responses, while changes in central nervous system activity can modify intestinal function.

The GBA concept is particularly relevant to IBS because the disorder involves abnormalities at both peripheral and central levels. Peripheral changes may include altered intestinal motility, epithelial permeability, immune signaling, microbial composition, and sensory nerve activity. Central mechanisms include altered pain processing, emotional regulation, stress responsiveness, and autonomic control [1,3].

This bidirectional system can create feedback loops. For example, psychological stress may alter intestinal physiology and increase visceral sensitivity, while persistent abdominal pain and unpredictable bowel symptoms may subsequently increase psychological distress. Thus, IBS may be maintained by reciprocal interactions between gastrointestinal and central mechanisms rather than by a single pathological abnormality.

3. Stress Signaling and the HPA Axis

Psychological and physiological stress are important modulators of gastrointestinal function. Stress activates the HPA axis and sympathetic nervous system, resulting in the release of corticotropin-releasing hormone, adrenocorticotropic hormone, and glucocorticoids. These mediators can influence intestinal motility, secretion, epithelial permeability, immune activity, and visceral sensory processing.

The relationship between stress and IBS is bidirectional. Stress may precipitate or aggravate gastrointestinal symptoms, while recurrent gastrointestinal symptoms can contribute to psychological distress and further activation of stress pathways. Recent evidence also indicates that different stress paradigms can produce intestinal barrier impairment, low-grade inflammation, microbial alterations, and changes in neural signaling relevant to IBS [4].

The HPA axis may therefore represent an important interface between psychological experiences and gastrointestinal physiology. Repeated or prolonged stress signaling can potentially modify intestinal homeostasis and sensory processing, contributing to symptom amplification.

Stress may also influence intestinal immune cells. Mast cells are positioned close to enteric and sensory nerves and can respond to neuroendocrine signals associated with stress. Their mediators can influence epithelial permeability, intestinal secretion, motility, and sensory signaling [5].

Recent literature on the stress–microbiota–brain relationship further suggests that stress can modify microbial communities, while microbial alterations and microbial metabolites may influence stress responsiveness and neurological signaling [6].

4. Gut Microbiota and Microbiota–Brain Communication

The intestinal microbiota is an important component of the GBA. Microorganisms interact with intestinal epithelial cells, immune cells, enteric neurons, and host metabolic pathways. Microbial products can consequently influence intestinal and systemic physiology.

Alterations in microbial composition have been reported in IBS, although a single reproducible microbial signature has not been established. Differences between studies may arise from variations in diet, geography, medication exposure, IBS subtype, disease severity, sample collection, and analytical methodology.

Potential consequences of microbiota alterations include changes in fermentation, production of short-chain fatty acids (SCFAs), bile-acid metabolism, intestinal permeability, immune activity, and neural signaling. SCFAs such as acetate, propionate, and butyrate can influence epithelial integrity and immune responses and may also participate in signaling between the gut and nervous system.

The microbiota may additionally interact with neurotransmitter-related pathways. Microbial and host-derived neurotransmitter systems can influence intestinal motility, secretion, immune activity, and microbial homeostasis, providing another potential route through which intestinal changes may affect brain–gut communication [7].

Recent systematic evidence supports alterations in the intestinal microbiota among patients with IBS, but substantial heterogeneity remains. Therefore, dysbiosis should be regarded as one component of IBS pathophysiology rather than a universal abnormality present in every patient.

5. Intestinal Barrier Dysfunction

The intestinal epithelium forms a selective barrier between luminal contents and the internal environment. Tight-junction complexes regulate paracellular permeability and help prevent inappropriate exposure of subepithelial tissues to luminal antigens and microbial products.

Altered intestinal permeability has been identified in subsets of patients with IBS. A systematic review examining intestinal barrier function identified substantial evidence for barrier abnormalities, while also highlighting differences according to IBS subtype, methodology, and study population [8].

Stress may influence epithelial integrity through neuroendocrine and immune pathways. Conversely, increased exposure of mucosal tissues to microbial or dietary components may activate immune and sensory pathways. Barrier dysfunction may therefore provide a mechanistic link between stress, microbiota alterations, mucosal immune activity, and visceral hypersensitivity.

However, intestinal permeability abnormalities are not universal in IBS. This variability reinforces the concept that IBS comprises multiple biological phenotypes rather than a single disease mechanism.

6. Neuroimmune Signaling and Mast Cells

Low-grade immune activation has been described in subsets of patients with IBS. Among immune cells, mast cells have received considerable attention because of their anatomical proximity to intestinal sensory nerves and their ability to release multiple bioactive mediators.

Mast cells can be activated by microbial products, food-related factors, immune signals, and stress-associated pathways. Following activation, they can release histamine, tryptase, prostaglandins, and cytokines. These mediators may influence epithelial permeability and activate or sensitize sensory neurons [5,9].

The close relationship between mast cells and sensory nerves provides a potential mechanism connecting intestinal immune activity with abdominal pain. Mast-cell mediators can increase neuronal excitability and contribute to visceral hypersensitivity, particularly in selected patient populations.

Recent research has further examined the mast-cell–protease-activated receptor 2 (PAR2)–transient receptor potential (TRP) pathway as a possible convergent mechanism of visceral hypersensitivity. Mast-cell-derived tryptase can activate PAR2, which can subsequently sensitize TRP channels involved in nociceptive signaling [10].

These findings provide a potential pharmacological basis for investigating mast-cell stabilizers, histamine receptor antagonists, protease signaling inhibitors, and related approaches. However, these therapies remain mechanistically targeted and should not be considered universally established treatments for IBS.

7. Visceral Hypersensitivity and Pain Processing

Visceral hypersensitivity is an important mechanism underlying abdominal pain in IBS. Patients may experience exaggerated responses to intestinal distension or other physiological stimuli that would normally produce little or no discomfort.

Peripheral sensitization may arise from interactions among epithelial, immune, microbial, and neuronal pathways. Inflammatory mediators, mast-cell products, and altered intestinal permeability can influence sensory afferent excitability.

Central mechanisms are also important. Repeated visceral stimulation may alter spinal and supraspinal pain-processing pathways, while psychological factors such as stress, anxiety, and hypervigilance can influence the perception of visceral stimuli.

Earlier mechanistic studies identified alterations in peripheral sensory pathways and inflammatory mediators as contributors to visceral hypersensitivity [11]. More recent work continues to investigate the molecular pathways underlying sensory sensitization, including TRP channels, protease signaling, and histamine-mediated mechanisms [10,12].

Thus, abdominal pain in IBS should be viewed as the result of interactions between peripheral sensory signaling and central modulation rather than simply increased intestinal contractions.

8. Neurotransmitters and the Gut–Brain Axis

Neurotransmitters participate in communication between the gastrointestinal tract and central nervous system. Serotonergic, cholinergic, dopaminergic, and GABAergic pathways can influence gastrointestinal motility, secretion, immune function, and sensory processing.

Serotonin is particularly relevant because gastrointestinal serotonergic signaling participates in intestinal motility and secretion and can influence visceral sensory pathways. Altered neurotransmitter signaling may therefore contribute to differences in bowel habits and symptom perception.

Microbiota–neurotransmitter interactions provide an additional layer of complexity. Microbial activity can influence the availability and metabolism of compounds involved in neurotransmitter pathways, whereas host neurotransmitters can also affect microbial and intestinal functions [7].

However, neurotransmitter alterations should not be considered a single defining abnormality in IBS because the contribution of specific signaling pathways may differ between patients and IBS subtypes.

9. IBS Subtypes and GBA Dysregulation

IBS is clinically divided into IBS-C, IBS-D, IBS-M, and IBS-U according to predominant stool patterns.

Although these subtypes share mechanisms such as altered visceral sensitivity and brain–gut communication, the relative contribution of motility, secretion, microbial metabolism, bile-acid handling, barrier dysfunction, and sensory pathways may differ. This heterogeneity is important when interpreting studies of IBS pathophysiology. A treatment that primarily modifies intestinal transit may have limited effects in a patient whose predominant mechanism is visceral hypersensitivity or stress-associated symptom amplification.

Consequently, future approaches to IBS management may increasingly incorporate biological and physiological phenotyping in addition to conventional symptom classification.

10. Therapeutic Opportunities Targeting the Gut–Brain Axis

10.1 Dietary interventions

Dietary management remains an important component of IBS treatment. General dietary advice may include regular meals, appropriate fiber intake, adequate hydration, and identification of individual food triggers.

The low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (low-FODMAP) diet has been investigated extensively. A systematic review and network meta-analysis found evidence supporting its short-term effectiveness for global IBS symptoms and abdominal symptoms [13].

However, the low-FODMAP diet is not simply a permanent restrictive diet. Structured implementation, followed by dietary reintroduction and personalization, is important to minimize unnecessary dietary restriction and potential effects on nutritional adequacy and microbial diversity.

10.2 Pharmacological treatment

Pharmacological treatment is generally selected according to the predominant IBS symptoms and subtype.

For IBS-C, pharmacological options include osmotic laxatives, intestinal secretagogues, and other agents that improve bowel evacuation. The American Gastroenterological Association guideline provides evidence-based recommendations for agents including linaclotide, plecanatide, lubiprostone, tenapanor, tegaserod, and other therapies [14].

For IBS-D, treatment options include rifaximin, loperamide for diarrhea control, bile-acid-directed approaches in selected patients, and other symptom-specific therapies. The American Gastroenterological Association guideline provides recommendations for pharmacological management of IBS-D [15].

The American College of Gastroenterology guideline also supports a positive diagnostic strategy and recommends selected dietary, pharmacological, and gut-directed psychological approaches according to patient presentation [16].

10.3 Neuromodulators

Neuromodulators can influence visceral pain processing and communication between the gut and brain. Tricyclic antidepressants are used in selected patients, particularly when abdominal pain is prominent.

Their therapeutic effects in IBS are not necessarily dependent on treatment of a psychiatric disorder. At appropriate doses, these drugs may alter central pain processing and gastrointestinal sensory pathways.

The evidence base for antidepressant therapy has expanded over time, and recent meta-analytic evidence continues to support potential benefits for overall IBS symptoms and abdominal pain, although heterogeneity and publication bias should be considered [17].

10.4 Gut-directed psychological therapies

Because stress and altered central pain processing are important components of IBS, psychological interventions can directly target GBA dysfunction.

Cognitive behavioral therapy (CBT), gut-directed hypnotherapy, and related approaches have demonstrated improvements in IBS symptoms in randomized clinical trials. A network meta-analysis of 41 randomized trials involving more than 4,000 participants found evidence supporting several psychological approaches, particularly CBT-based interventions and gut-directed hypnotherapy, while also noting limitations in trial quality [18].

More recent systematic evidence continues to support psychological therapies as useful components of IBS management, although treatment effects vary and substantial heterogeneity exists among interventions and patient populations [19].

These interventions should not be interpreted as evidence that IBS symptoms are purely psychological. Rather, they target established pathways involving stress responsiveness, central pain processing, behavioral responses, and brain–gut communication.

10.5 Probiotics, prebiotics, and synbiotics

Microbiota-directed approaches have attracted considerable attention because of the potential role of microbial alterations in IBS.

Probiotics may influence intestinal microbial composition, epithelial barrier function, immune signaling, and microbial metabolites. However, effects are often strain-specific, and different formulations may produce different outcomes.

A recent systematic review and network meta-analysis evaluated probiotics, prebiotics, synbiotics, and FMT in IBS, illustrating both the potential and heterogeneity of microbiota-directed interventions [20].

Therefore, rather than considering “probiotics” as a single therapeutic category, future research should

identify specific strains, combinations, doses, and patient phenotypes associated with reproducible clinical responses.

10.6 Fecal Microbiota Transplantation

Fecal microbiota transplantation (FMT) attempts to modify the intestinal microbial ecosystem by transferring microbiota from a screened donor to a recipient.

Clinical trials of FMT in IBS have produced inconsistent results. A systematic review and meta-analysis found insufficient evidence to establish FMT as a routine treatment, with substantial heterogeneity among studies [21].

A later systematic review and trial-sequential analysis similarly demonstrated uncertainty regarding the clinical efficacy of FMT, emphasizing the importance of donor selection, delivery route, treatment protocol, and patient characteristics [22].

FMT should therefore be regarded as an investigational microbiome-directed strategy rather than an established standard therapy for IBS.

10.7 Psychobiotics and microbial metabolites

The concept of psychobiotics has emerged from research investigating microorganisms and microbial products that may influence psychological and neurological processes.

Potential mechanisms include modulation of SCFAs, tryptophan metabolism, immune signaling, intestinal permeability, HPA-axis activity, and neurotransmitter-related pathways.

Although the concept is scientifically promising, clinical evidence remains insufficient to identify a universally effective psychobiotic intervention. Future studies should move beyond broad descriptions of microbial abundance and investigate functional microbial pathways and metabolites.

10.8 Vagus Nerve Stimulation and Neuromodulation

The vagus nerve represents a potential therapeutic target because it participates in bidirectional gut–brain communication and neuroimmune regulation.

Vagus nerve stimulation and other neuromodulation techniques are being investigated for their ability to influence autonomic activity, inflammatory signaling, and pain processing. Recent reviews have highlighted neuromodulation as an emerging approach for disorders involving GBA dysfunction, including IBS [23,24].

However, clinical evidence remains insufficient to establish neuromodulation as routine IBS therapy. Larger, well-controlled trials are needed to determine appropriate stimulation parameters, patient selection, treatment duration, and long-term efficacy.

11. Emerging Mechanism-Based Therapeutic Targets

11.1 Mast-cell pathways

Mast-cell stabilization and inhibition of mast-cell mediators may be relevant to patients with evidence of mast-cell-associated visceral hypersensitivity. Histamine receptor antagonism and mast-cell stabilizers have been investigated, although clinical benefits have generally been modest and inconsistent [9,12].

11.2 PAR2 and TRP channels

The mast-cell–PAR2–TRP pathway represents an emerging target because of its potential role in sensory neuronal sensitization. Pharmacological modulation of these pathways may provide future approaches for treating visceral pain [10].

11.3 Microbial metabolites

Microbial metabolites, including SCFAs, bile-acid derivatives, and tryptophan metabolites, may represent more specific therapeutic targets than broad manipulation of microbial composition. Modifying microbial metabolic functions could potentially influence epithelial integrity, immune responses, and neural signaling.

11.4 Vagal and autonomic pathways

Modulation of vagal activity may provide another approach to restoring communication between the gastrointestinal tract and brain. This strategy is particularly relevant because the vagus nerve integrates neural and immune signals within the GBA [23].

12. From Symptom-Based to Mechanism-Based Treatment

A major challenge in IBS management is the heterogeneity of underlying mechanisms. Patients with the same clinical diagnosis may have different combinations of motility abnormalities, visceral hypersensitivity, barrier dysfunction, microbial alterations, immune activation, and psychological stress.

This heterogeneity supports a move toward mechanism-based treatment. Potential biological phenotypes could include stress/HPA-axis-associated IBS; visceral hypersensitivity-predominant IBS; microbiota-associated IBS; intestinal barrier dysfunction-associated IBS; neuroimmune or mast-cell-associated IBS; and motility-predominant IBS. These categories should currently be regarded as conceptual rather than universally validated clinical classifications.

Future precision-medicine approaches may integrate clinical phenotype with microbiome composition, metabolomic profiles, intestinal permeability, immune markers, autonomic measurements, psychological characteristics, and sensory testing.

13. Challenges and Future Perspectives

Despite substantial progress in understanding the GBA, several challenges remain. IBS lacks a single biomarker capable of reliably identifying all patients

or determining the dominant mechanism in an individual patient. Microbiome findings also vary considerably across studies because of differences in diet, geography, medications, sampling methods, and analytical platforms.

Another limitation is that many mechanistic findings demonstrate associations rather than causality. Animal models have provided important information regarding stress-induced visceral hypersensitivity, barrier dysfunction, and microbiota changes, but they cannot completely reproduce the complex behavioral and psychosocial environment of human IBS.

Future research should therefore combine microbiomics, metabolomics, neuroimaging, immune profiling, autonomic measurements, and clinical phenotyping. Such multidimensional approaches may help identify biologically meaningful patient subgroups.

Artificial intelligence and machine-learning approaches may further assist in integrating large datasets and identifying patterns associated with treatment response. However, these approaches require validation in diverse populations before routine clinical application.

The future of IBS therapy is therefore likely to involve a combination of symptom-directed treatment and mechanism-based interventions rather than a single universal therapy.

14. Conclusion

IBS is a complex disorder of gut–brain interaction involving reciprocal communication between the gastrointestinal tract and the central nervous system. Stress-related activation of the HPA axis and autonomic pathways can influence intestinal motility, epithelial integrity, immune signaling, microbial composition, and visceral sensitivity. In parallel, intestinal microbial metabolites, immune mediators, and sensory signals can influence central pathways involved in stress, emotion, and pain processing.

Gut dysbiosis, intestinal barrier dysfunction, mast-cell activation, neuroimmune signaling, and visceral hypersensitivity should therefore be viewed as interconnected components of IBS pathophysiology rather than isolated abnormalities. This integrated model helps explain the clinical heterogeneity of IBS and the variable response to individual treatments.

Current management includes dietary modification, pharmacological therapy, neuromodulators, microbiota-directed interventions, and gut-directed psychological therapies. Emerging strategies involving psychobiotics, microbial metabolites, mast-cell pathways, vagal stimulation, and neuromodulation may provide additional therapeutic opportunities, although several remain investigational.

A deeper understanding of GBA dysfunction may facilitate the transition from predominantly symptom-based management toward individualized, mechanism-based treatment. Integration of gastroenterology, neuroscience, microbiology, immunology, pharmacology, and behavioral science will be essential for translating advances in GBA research into clinically useful therapies.

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