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REVIEW

Exploring the Mechanisms of Gastroesophageal Reflux Disease Based on the Brain-Gut Axis Theory

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Abstract: Gastroesophageal reflux disease (GERD) is a common clinical digestive disorder with a complex pathological mechanism. Traditional understanding of its mechanisms primarily focuses on factors such as lower esophageal sphincter dysfunction, impaired esophageal clearance, delayed gastric emptying, and abnormal gastric acid secretion. In recent years, the introduction of the brain-gut axis (BGA) theory has provided a new perspective for the systematic understanding of GERD's pathogenesis. However, there remains a significant lack of understanding regarding the specific mechanisms of BGA in GERD, particularly in terms of the interactions between the nervous, endocrine, and immune systems, and how they influence the symptoms and progression of gastroesophageal reflux. This paper aims to review the abnormal mechanisms of the nervous, endocrine, and immune systems in GERD based on the BGA theory, clarify the relationships between these systems in the development of GERD, and explore the current gaps in knowledge and future research directions. Studies have shown that GERD patients often present with neurological abnormalities such as central nervous system hypersensitivity, autonomic nervous imbalance, and enteric nervous system remodeling. Additionally, activation of the HPA axis and prolonged elevation of cortisol exacerbate esophageal injury, while local and systemic immune inflammation further induces visceral hypersensitivity, creating a stress-induced "neuroimmune loop". Based on the BGA mechanism, future individualized treatments for GERD, which integrate the regulation of central nervous function, endocrine levels, and the immune microenvironment, may provide new strategies and clinical interventions, leading to breakthroughs in relevant therapies.

Keywords: GERD, BGA, pathogenesis, nervous system, endocrine system, immune system

Introduction

GERD is a gastrointestinal motility disorder caused by the reflux of gastric contents into the esophagus. Its main symptoms include acid regurgitation, heartburn, chest pain, and cough, with some patients also experiencing dysphagia and hoarseness. GERD can lead to complications such as esophagitis, Barrett's esophagus, and even esophageal adenocarcinoma, significantly impacting the patient's quality of life and social functioning. Due to the fast-paced nature of modern life and dietary changes, the prevalence of GERD has been rising steadily. It is estimated that the global prevalence ranges between 8% and 33%,[1] making it a major global public health concern. The mechanisms underlying GERD have not yet been fully understood in traditional medicine, although it is generally believed to be the result of multiple contributing factors, including decreased lower esophageal sphincter (LES) pressure, delayed gastric emptying, impaired esophageal clearance, and compromised esophageal mucosal defense mechanisms.[2] However, although these traditional mechanisms are important for explaining the pathophysiology of GERD, they remain limited. In some patients, symptoms do not correspond to the organic changes observed under endoscopy,[3] and conventional treatment strategies such as proton pump inhibitors (PPIs) are ineffective for a subset of patients. This suggests that the etiology of GERD is not confined to local anatomical or functional abnormalities. These limitations highlight the need to understand

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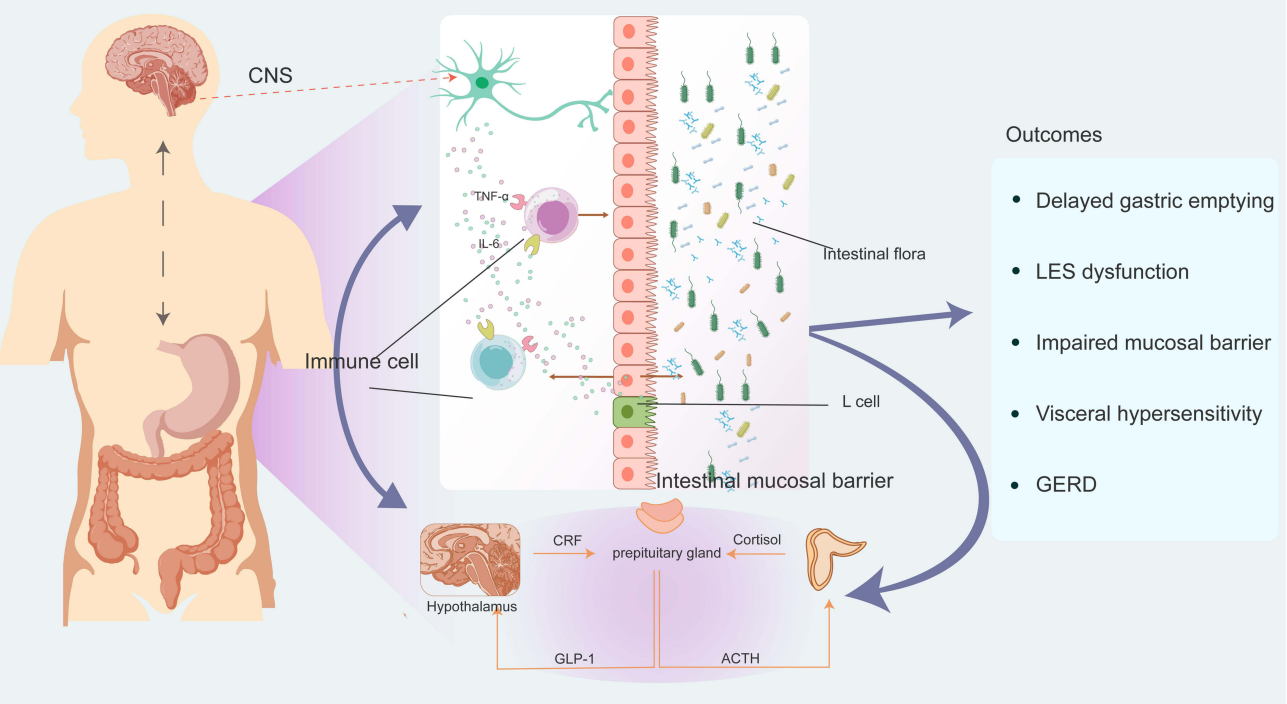

Figure 1 The relationship between GERD and the brain–gut axis (BGA)-mediated neuroendocrine–immune system.

the pathogenesis of GERD from a broader perspective. In recent years, BGA theory has gradually attracted attention and emerged as a potential explanatory framework. The BGA regulates gastrointestinal function, emotional responses, and stress reactions through multiple signaling pathways involving neural, endocrine, and immune systems. Studies have reported[4] that in some GERD patients, the relationship between symptoms and organic changes is weak, with a portion of these patients also experiencing varying degrees of anxiety and depression. Research based on the BGA theory not only deepens our understanding of the mechanisms underlying GERD and fills existing knowledge gaps, but may also provide new therapeutic approaches. In particular, for patients who do not respond to conventional therapies, the regulatory mechanisms of the BGA may represent important intervention targets (Figure 1).

Brain-Gut Axis

BGA refers to a bidirectional communication system constructed through neural, endocrine, and immune pathways among the central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), and gut microbiota. This integrated network coordinates brain and gut functions, effectively maintaining gastrointestinal motility, stress response regulation, internal homeostasis, as well as emotional and cognitive balance.[5] Various studies have confirmed that abnormal brain-gut interactions and alterations in the gut microenvironment are closely associated with GERD.

Interactions Within the Brain-Gut Axis and an Integrated Perspective

The BGA is a complex, interconnected, and dynamically regulated communication network. It is not merely a simple bidirectional link between the brain and the gut but a comprehensive regulatory system interwoven across multiple systems and signaling pathways. Under stress conditions, the CNS integrates emotional and stress-related signals via key regions such as the cerebral cortex, limbic system, and hypothalamus, subsequently activating the hypothalamic-pituitary -adrenal (HPA) axis. This activation promotes the gene expression and protein synthesis of corticotropin-releasing factor (CRF), which then stimulates the adrenal cortex to secrete cortisol. As a critical endocrine signaling molecule, cortisol modulates gastrointestinal motility, gastric acid secretion, and mucosal barrier protection.[6] CRF can directly reduce lower esophageal sphincter (LES) pressure, delay gastric emptying, and increase visceral sensitivity.

The ANS modulates gastrointestinal motility and secretion via the vagus and sympathetic nerves, regulating the release of hormones such as gastrin and cholecystokinin to achieve rapid and precise functional adjustments.[7] The ENS, through the myenteric and submucosal plexuses, independently governs intestinal motility patterns, secretory activity, and sensory signaling. It also interacts with afferent and efferent signals from the CNS, enabling integration of local and systemic functions.[8,9]

Endocrine and immune pathways act as chemical amplifiers of these signals. Gut-associated lymphoid tissue (GALT) and local immune cells can detect external stimuli and release inflammatory mediators such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). These inflammatory signals not only cause local mucosal barrier dysfunction and increased intestinal permeability but can also be transmitted to the CNS via humoral circulation or the vagus nerve. This feedback promotes microglial activation, enhances pain sensitivity, and contributes to emotional disturbances, leading to a state of visceral hypersensitivity.[9]

Moreover, gut-derived hormones such as glucagon-like peptide-1 (GLP-1) can delay gastric emptying, influence sphincter contraction, and modulate central emotional responses. Collectively, the neural, immune, and endocrine mechanisms are intricately intertwined, forming the core regulatory loop that underpins the communication and feedback within the BGA.

Relationship Between the Brain-Gut Axis and Gut Microbiota

The gut microbiota (GM), a complex and heterogeneous ecological community composed of bacteria, archaea, fungi, protozoa, parasites, and viruses, has been increasingly recognized for its critical role in human health.[10] More than 99% of bacterial species belong to the phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria, among which Firmicutes and Bacteroidetes dominate in the gut microbiota of healthy hosts.[11] The ratio of Firmicutes to Bacteroidetes is considered an important indicator for assessing the stability of microbial composition.[12] Firmicutes secrete a variety of glycosidases that degrade polysaccharides indigestible to humans into short-chain fatty acids (SCFAs), thereby regulating energy absorption while maintaining intestinal epithelial integrity and contributing to gut barrier protection.[13] Bacteroidetes not only meet host nutritional demands by efficiently metabolizing complex polysaccharides and participating in bile acid circulation, but also help maintain gut microbiota stability through colonization resistance and immune modulation. Emerging evidence[14] suggests that the maternal-offspring connection during embryonic development establishes a close relationship between the gut microbiota and the host, influencing fetal brain development and psychological health. The interactions between the gut microbiota and the brain involve multiple intricate pathways. Alterations in the gut microbiota can directly impact the gut immune system, as certain microbes can synthesize or produce gut-associated metabolites, neuroactive modulators, and other molecules.[8] Among these, short-chain fatty acids (SCFAs) have been studied most extensively.

SCFAs, including acetate, propionate, and butyrate, are major metabolites produced in the gut through the fermentation of dietary fiber by anaerobic bacteria. SCFAs can cross the blood-brain barrier and modulate neuroinflammation and brain cell metabolism.[15] Butyrate, in particular, affects BGA function through multiple mechanisms. As a histone deacetylase (HDAC) inhibitor, butyrate alters gene expression in intestinal epithelial cells, promotes the synthesis of tight junction proteins, strengthens the intestinal barrier, and reduces the translocation of gut-derived toxins into the bloodstream, thereby indirectly protecting the central nervous system.[16,17] Additionally, butyrate can enter the brain via systemic circulation, attenuate microglial activation and the release of pro-inflammatory cytokines, modulate inflammatory cytokines and signaling pathways in primary astrocyte cultures, and promote the synthesis of γ-aminobutyric acid (GABA), exerting anxiolytic and antidepressant effects.[18,19] Compared with healthy individuals, patients with non-erosive reflux disease (NERD) and those with emotional disorders exhibit an increased abundance of Firmicutes and a decreased abundance of Bacteroidetes. Moreover, the diversity and composition of the gut microbiota are closely associated with anxiety and depression, suggesting that the BGA may play an important role in the pathogenesis of GERD.

Tryptophan metabolites also play a crucial role in BGA regulation. Gut microbiota can convert tryptophan into metabolites such as 5-hydroxytryptamine (5-HT, serotonin) and kynurenine. Among these, 5-HT serves as a key node connecting the brain-gut-microbiota axis. Approximately 95% of 5-HT is synthesized in the gut, and gut microbes regulate its production by modulating the activity of tryptophan hydroxylase 1 (TPH1), the rate-limiting enzyme for

5-HT synthesis. Alterations in gut microbiota composition can affect TPH1 activity and thereby influence 5-HT levels.[20] Germ-free animal models have played an essential role in elucidating the functions of GM; for example, germ-free male mice show decreased colonic 5-HT production and elevated hippocampal 5-HT levels.[21,22]

Furthermore, 5-HT promotes the release of acetylcholine from enteric nervous system (ENS) neurons and activates vagal afferent fibers, thereby regulating gastrointestinal motility. It can also activate transient receptor potential vanilloid 1 (TRPV1) channels, altering visceral pain thresholds, and participate in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis and stress responses.[23,24] In addition to 5-HT synthesis, gut microbiota can modulate the production of other neurotransmitters such as GABA and catecholamines, thereby influencing vagal activity and neural development. These effects directly or indirectly impact neural signaling within the BGA, shaping excitatory and inhibitory pathways in esophageal neurons.[25] As a result, they modulate lower esophageal sphincter motility and may exacerbate GERD symptoms.

Therefore, SCFAs and tryptophan serve as critical substrates for bidirectional communication between the brain and the gut. Their unique physiological property lies in their high permeability across both the intestinal barrier and the blood–brain barrier, enabling them to freely transit among the gut, circulation, and central nervous system. This property allows SCFAs to exert multidimensional regulatory effects: they can directly or indirectly influence circulatory function and peripheral tissue metabolism, while also modulating the functional states of various central cell types, such as microglia, thereby playing a pivotal role in processes closely related to neuroinflammation and neurological health. In addition, evidence suggests that SCFAs not only exert fundamental physiological effects locally within the gut but also transmit signals systemically via circulation or neural pathways, exerting regulatory influences on the brain and multiple organ systems.[26] These findings, supported by both animal and human studies, indicate that dysbiosis of the gut microbiota is associated with behavioral and neurological disorders such as autism and Parkinson's disease.[27–29] Furthermore, strategies targeting the modulation of the gut microbiota (eg, probiotics and fecal microbiota transplantation) as well as exogenous supplementation with SCFAs have been widely proposed as potential therapeutic approaches, offering new avenues for mechanism-based interventions.[15]

The BGA links the enteric nervous system (ENS) and the central nervous system (CNS) via the hypothalamic–pituitary–adrenal (HPA) axis, thereby driving the endocrine system to release hormones such as cortisol, which in turn exert bidirectional interactions with the gut immune system. The function of the gut immune system depends on the integrity of the mucosal barrier, the homeostasis of immune cells, and the balance of the gut microbiota, which also maintains a unique bidirectional regulatory relationship with the BGA. Collectively, the nervous, endocrine, and immune systems form a multidimensional cross-regulatory network through the BGA, and its dysfunction represents a key mechanism in the development of GERD. CNS, central nervous system; CRF, corticotropin-releasing factor; ACTH, adrenocorticotropic hormone; LES, lower esophageal sphincter; GERD, gastroesophageal reflux disease.

Neural Regulation Mechanisms: Abnormalities in the Central-Autonomic-Enteric Nervous Axis

In recent years, studies have shown that the brain-gut axis (BGA) plays a critical role in the pathogenesis and progression of GERD, with particular emphasis on the dysregulation and remodeling of neural regulatory systems. This has become one of the core mechanisms explaining the diversity of symptoms and treatment resistance.

Effects of the Central Nervous System (CNS)

The CNS serves as the highest regulatory center of the BGA, sensing gastrointestinal signals and modulating descending neural reflexes and stress responses via the hypothalamic-pituitary-adrenal (HPA) axis and regions such as the locus coeruleus, prefrontal cortex, insular cortex, and cingulate gyrus.[30] Clinically, GERD patients frequently exhibit emotional disorders, including anxiety and depression, with symptom perception often disproportionate to the actual degree of acid reflux. This suggests abnormalities in central perception and processing. The association between emotional cognition and GERD symptoms is mediated partly through neuropeptides such as corticotropin-releasing factor (CRF), which regulate HPA axis activity, and partly through altered interactions between cortisol and the amygdala within central

networks. These processes promote further CRH secretion under stress, enhance central sensitization of stress pathways, and ultimately influence descending pain modulation and gastrointestinal motility.[31]

Li Zhaoshen and colleagues[32] found that patients with non-erosive reflux disease (NERD) exhibit heightened visceral sensitivity under stress, where even mild reflux stimuli can cause severe heartburn or chest pain. This abnormal visceral sensory pathway is closely related to central sensitization within the nucleus tractus solitarius-thalamus-cerebral cortex pathway.[33] By analyzing fMRI results,[32] significant abnormalities were observed in the brain activation patterns of GERD patients, particularly in the areas related to emotional regulation and gastrointestinal sensory control. Specifically, abnormal activation in the prefrontal cortex, insular cortex, and cingulate gyrus was closely associated with the perception of GERD symptoms and stress responses. These findings suggest that the role of the central nervous system in GERD is not only through the control of gastrointestinal motility but also through the modulation of emotional and stress responses, which enhances visceral hypersensitivity. However, most of these studies have focused on brain region activation, lacking in-depth analysis of the interactions between different brain areas. Future studies could apply the wireless, non-invasive electroencephalography (EEG) signal acquisition technology developed by the team of Tianzi Jiang, which, from the perspective of EEG topography, utilizes the spatiotemporal characteristics of microstate signals to explore the functional division and network connectivity between different brain regions in the circuitry. Furthermore, investigating how these regions exhibit differential expressions in various GERD subtypes (eg, non-erosive reflux disease, NERD) could provide precise molecular targets for targeted interventions.

Autonomic Nervous System (ANS) Dysfunction

The ANS, composed of sympathetic and parasympathetic branches, plays a crucial role in modulating gastrointestinal motility and secretion, with the vagus nerve being particularly important for regulating lower esophageal sphincter (LES) tone, gastric emptying, and salivary secretion.[34] GERD patients are frequently characterized by an imbalance between sympathetic and parasympathetic tone, a dysregulation that suppresses gastrointestinal function and delays gastric emptying, thereby increasing intragastric pressure and creating favorable conditions for reflux.[35] This ANS dysfunction is particularly pronounced in patients with NERD, where the severity of symptoms is often positively correlated with the degree of sympathetic–parasympathetic imbalance.[36]

Imaging studies have shown a close relationship between heart rate variability (HRV) and the prefrontal cortex,[37] regions involved in pain perception and stress evaluation. HRV provides valuable insights into the impact of ANS dysregulation on GERD and serves as an objective indicator of mental health status and stress levels.[38] Studies[39] have shown that GERD patients with lower HRV values exhibit a decrease in parasympathetic components and an increase in sympathetic components, indicating vagal dysfunction. Under chronic stress, CRF release enhances sympathetic activity, leading to decreased gastrointestinal blood flow, inhibited motility, and increased inflammation.[40] Sympathetic overactivation can further suppress vagal activity, creating a vicious cycle of "stress–ANS imbalance–gastrointestinal dysfunction–exacerbated inflammation". This pathway also constitutes an important branch of the stress-induced "neuro-immune loop".

Enteric Nervous System (ENS) Remodeling

The ENS, often referred to as the "second brain", is an extensive reflex control system for digestive functions. Working in concert with the CNS and sympathetic ganglia,[41] it plays a key role in integrating local gastrointestinal information, allowing for significant autonomy in gut function. The ENS resides within the muscular layers of the gastrointestinal tract, containing a number of neurons comparable to that in the spinal cord.[42] The myenteric plexus, located between the longitudinal and circular muscle layers and extending from the esophagus to the rectum, spans the entire digestive tract.

Imbalances in neurotransmitters within the ENS, such as acetylcholine (Ach), nitric oxide (NO), and vasoactive intestinal peptide (VIP),[43] can affect sphincter tone. Ach, an excitatory neurotransmitter in the ENS, promotes smooth muscle motility and inhibits NO. Conversely, NO acts as an inhibitory neurotransmitter related to LES relaxation;[44] excessive NO release can lower LES pressure, while Ach dysfunction reduces gastrointestinal peristalsis. Thus, ENS dysfunction may lead to reflux and delayed gastric emptying.[45]

In patients with reflux-induced inflammation, the number of ENS neurons in the distal esophagus is reduced and nerve fibers undergo degeneration, thereby enhancing local neuroinflammation. Moreover, some studies have indicated[46]

that structural remodeling of the ENS may increase the sensitivity of local nerve endings, leading patients to experience stronger pain and discomfort in response to reflux stimuli.

In summary, the neural dysregulation of GERD exhibits a synergistic pattern characterized by "central sensitization–autonomic imbalance–enteric remodeling". This mechanism provides new targets and perspectives for clinical intervention. At the diagnostic level, HRV may serve as a non-invasive indicator for assessing ANS dysfunction. Combined with BOLD-fMRI or novel electroencephalographic techniques (eg, wireless wearable EEG acquisition devices) to monitor CNS activation and network connectivity, it holds promise for achieving precise subtyping of GERD.[47,48] For instance, the degree of HRV reduction, together with abnormal EEG microstate patterns, could help distinguish between "ANS-dominant" and "central sensitization" subtypes of NERD, thereby providing a rationale for individualized treatment.

Endocrine Mechanisms: Stress Hormones and Gastrointestinal Motility Regulation

Within the brain-gut axis (BGA), the endocrine pathway serves as a crucial link between the central nervous system and gastrointestinal function. This pathway mainly includes the hypothalamic-pituitary-adrenal (HPA) axis and hormones released by gut endocrine cells,[49] such as corticotropin-releasing factor (CRF), cortisol (CORT), and glucagon-like peptide-1 (GLP-1). Dysregulated secretion of these hormones represents a central component of hormonal regulation within the stress-induced "neuro-immune loop".

Crf

CRF, a neuropeptide secreted by the paraventricular nucleus (PVN) and arcuate nucleus of the hypothalamus, initiates the stress response of the HPA axis.[50] During psychological or physical stress, CRF expression is upregulated, which activates pituitary secretion of adrenocorticotropic hormone (ACTH), further stimulating the adrenal cortex to release CORT—this represents the classical HPA axis pathway.[5] Meanwhile, CRF stimulates sympathetic activity via the locus coeruleus in the brainstem, promoting the release of norepinephrine (NE) from sympathetic neurons and epinephrine (E) from the sympathetic-adrenal medulla.[51] NE and E activate the sympathetic nervous system, decrease LES tone, increase transient relaxations, inhibit antral contractions via β-receptors, elevate intragastric pressure, and facilitate reflux.

CRF acts primarily within the PVN, ventromedial hypothalamus, and lateral hypothalamus. The ANS mediates CRF-induced gastric inhibition; animal studies[52] have shown that intracerebral CRF injection can induce delayed gastric emptying and gastrointestinal dysmotility, exacerbating GERD-related functional symptoms. CRF overexpression affects the dorsal motor nucleus of the vagus, suppresses parasympathetic output, reduces LES tone, slows esophageal peristalsis, and prolongs esophageal clearance time, thereby promoting reflux. Additionally, CRF enhances spinal and cortical sensitivity to visceral signals, participating in the modulation of visceral hypersensitivity. By activating CRF receptors in the brainstem and limbic system, CRF strengthens pain transmission pathways, leading to pronounced heartburn and chest pain even with mild stimulation.

Cort

CORT, the final effector molecule of HPA axis activation, is released from the adrenal cortex and serves as a stress-sensitive hormone.[53] CORT plays a key regulatory role in immune and inflammatory responses, energy metabolism, and emotional regulation.[54] Studies[55] have shown that under stress, the amygdala becomes hypersensitive to danger signals, leading to sustained HPA axis activation and continuous elevation of CORT. This contributes to central sensitization of pain pathways, promotes visceral afferent sensitization, and induces neurogenic inflammation.[56]

CORT can activate TRPV1/TRPA1 receptors through oxidative stress or direct receptor interactions, trigger calcitonin gene-related peptide (CGRP) release, promote histamine secretion, impair gastric mucosal barrier function, increase gastric acid permeability, and enhance sensitivity to reflux stimuli. Furthermore, it affects the expression of tight junction proteins in intestinal epithelial cells,[57] facilitating GERD development. Although acute, short-term CORT elevation has anti-inflammatory effects, chronic stress disrupts negative feedback regulation, leading to increased levels of inflammatory cytokines such as IL-6 and TNF-α, exacerbating esophageal mucosal damage and neural sensitivity.[58] However, it

remains unclear whether there are cell-specific targets mediating the interactions between CORT and inflammatory cytokines such as IL-6 and TNF-α.

Glp-1

GLP-1 is an intestinal hormone secreted by L cells in the small intestine. L cells express the surface receptor TGR5, and TGR5 agonists such as 6α-ethyl-23(S)-methylcholic acid (EMCA, INT-777) can induce GLP-1 release, modulating insulin secretion and delaying gastric emptying.[59] GLP-1 acts as an important regulatory factor within the BGA, participating in various gastrointestinal functions. In the central nervous system, GLP-1 primarily originates from preproglucagon (PPG) neurons in the caudal nucleus of the solitary tract.[60] PPG neurons project to sympathetic spinal nuclei containing neurons immunoreactive for Ach and NO, collectively regulating gastrointestinal functions by delaying gastric emptying and reducing LES tone,[61] thus helping prevent rapid gastric content entry into the esophagus.

GLP-1 can also engage central receptors to modulate emotional responses and is closely related to the vagus nerve. Animal studies[61] have shown that central or peripheral administration of GLP-1 receptor agonists, such as Ex-4, increases ACTH and CORT levels in rats, activates the HPA axis, induces anxiety-like behavior, and impairs swallowing function.[62] Clinical studies[63] have demonstrated that a low-carbohydrate diet in patients with type 2 diabetes alters gut microbiota, elevates GLP-1 levels, and produces antidepressant effects after three months.

GLP-1 receptor agonists have been shown to protect gastrointestinal function; for example, liraglutide can modulate gut microbial diversity, protect gastric mucosa, and reduce visceral hypersensitivity.[64] GLP-1 exhibits a dual regulatory role in GERD pathogenesis: on one hand, it delays gastric emptying and inhibits acid secretion to protect against reflux; on the other, delayed gastric emptying may increase intragastric pressure and worsen reflux symptoms. Therefore, when using GLP-1 receptor agonists, it is essential to assess individual patient differences and select appropriate treatment strategies accordingly.

In summary, HPA axis hormones (CRF and CORT) and the gut-derived hormone GLP-1 interact through the "central–peripheral–gut" axis, forming the core endocrine regulatory network of GERD and deeply participating in stress-induced "neuro–immune circuits". The combined dysregulation of these factors provides a mechanistic explanation for the symptom diversity and subtype heterogeneity observed in GERD, linking neural, endocrine, and immune-inflammatory pathways through the "neuro–immune circuits" and offering systemic targets for clinical intervention. Unfortunately, the dose–response relationship between GLP-1 and the "neuro–immune circuits" remains unclear. Nevertheless, early identification of GERD-prone populations with aberrant activation of the "neuro–immune circuits" could be achieved by assessing GLP-1 levels and gut microbiota composition in patients with type 2 diabetes prior to treatment, enabling primary prevention through dietary or psychological interventions.[65]

Immune-Inflammatory Mechanisms: Systemic Low-Grade Inflammation and Mucosal Damage

The gastrointestinal tract is not only the site of digestion and absorption but also the body's largest immune organ, involved in immune responses and inflammatory processes. The development of GERD is often accompanied by the activation of both local and systemic immune responses, excessive secretion of inflammatory cytokines, and over-activation of immune cells, all of which contribute to the worsening of GERD symptoms. Abnormalities in immune cells, immune mediators, and the gastrointestinal barrier together constitute the immune effector branch of the stress-induced "neuro–immune circuits".

Immune Cells

Recent studies have shown a significant increase in immune cell infiltration in the esophageal mucosa of GERD patients, particularly T cells, B cells, and macrophages, which play a key role in the pathogenesis and progression of GERD. T cell infiltration, especially, is notably pronounced. The imbalance of T cell subsets is a crucial factor in the initiation, maintenance, and resolution of the inflammatory response in GERD. In animal reflux models, T cells infiltrate the submucosa before any tissue damage or other immune cell involvement,[66] with the activation and infiltration of CD4+ and CD8+ T cells

being significantly associated with esophageal inflammation. Research[67] indicates that GERD patients have an increased ratio of CD4+ and CD8+ T cells, which correlates positively with esophageal injury and pathological changes. The rise in CD8+ T cells may serve as a negative feedback mechanism regulating the inflammatory response to external stimuli.[68] Through cytotoxic mechanisms, CD8+ T cells damage the esophageal epithelium, further exacerbating esophageal injury. Although the specific role of B cells in gastrointestinal immunity remains unclear, they secrete immunoglobulins (eg, IgG, IgA) that participate in local immune responses. Antibodies produced by B cells can form immune complexes with esophageal antigens, intensifying reflux-related damage. Macrophages and dendritic cells initiate local inflammatory responses by secreting cytokines, increasing intestinal permeability,[69] and thus exacerbating acid reflux. Simultaneously, Th1 cells secrete IFN-γ, enhance macrophage activity, and promote IL-1β release, indirectly sensitizing esophageal sensory neurons.[70] Th2 cells release IL-4 and IL-13, inducing esophageal epithelial cells to secrete thymic stromal lymphopoietin (TSLP), which activates dendritic cells in the lamina propria and indirectly modulates neuroinflammation.[71,72]

Immune Factors

The chronic inflammatory state in GERD is often associated with abnormal expression of cytokines, such as TNF-α, IL-6, and IL-8. These cytokines regulate inflammatory responses through multiple pathways and influence disease pathogenesis; however, their precise role in GERD initiation and progression remains debated.

TNF-α is a pro-inflammatory cytokine that plays a significant role in immune and inflammatory responses. Under normal conditions, TNF-α is present at low levels in squamous epithelial cells, but its expression is markedly elevated in the esophageal and gastric mucosa of GERD patients.[73] Studies[74] have shown that TNF-α can amplify local inflammation by activating the NLRP3 inflammasome and inducing IL-1β secretion, while also binding to TNF-R1 on esophageal sensory neurons and activating the p38 MAPK pathway, thereby increasing the open probability of TRPA1 channels and enhancing mucosal sensitivity to refluxate.[75] Traditionally, TNF-α elevation has been considered an "inflammatory product" secondary to reflux stimulation, and TNF-α inhibition can alleviate GERD symptoms. However, basic research suggests that its aberrant expression may compromise mucosal barrier integrity, acting as a potential susceptibility factor for disease, although longitudinal studies clarifying the temporal relationship are lacking.

IL-6 levels are positively correlated with the severity of GERD symptoms. IL-6 not only activates immune cells but also inhibits the negative feedback mechanism of presynaptic α2-adrenergic receptors (α2-AR) on NE release,[76,77] removing sympathetic "brake" on the esophagus, leading to excessive NE release. This results in esophageal dysmotility and inflammation. Additionally, IL-6, through the JAK-STAT3 pathway, increases the phosphorylation of TRPV1 in dorsal root ganglion (DRG) neurons,[78] inducing visceral pain after gastrointestinal cytokine stimulation. In most cases, IL-6 functions as an intermediate mediator within the "reflux–inflammation–symptom" axis, but in refractory GERD it may act independently of reflux as a "pathological driver", although evidence on subtype-specific characteristics and targeted interventions remains limited.

IL-8, a representative chemokine, mainly promotes the migration and activation of neutrophils. Studies[79] have shown that IL-8 effectively recruits neutrophils and exacerbates esophageal mucosal inflammation, leading to esophageal injury and ulceration. Its elevated expression is closely associated with the development of reflux esophagitis and is generally considered a downstream effector in the inflammatory cascade.

Gastrointestinal Barrier

The gastrointestinal barrier consists of multiple layers, including the mucus layer, epithelial cell layer with tight junctions, and immune cells in the lamina propria.[80] Tight junction proteins between epithelial cells are critical for maintaining mucosal integrity and limiting pathogen invasion.[81] The function of the gastrointestinal barrier depends on the integrity of tight junctions between intestinal epithelial cells.[49,82] In GERD patients, the expression of tight junction proteins between gastrointestinal epithelial cells is reduced, leading to increased gastrointestinal permeability.[83] This "leaky gut" allows pathogens, toxins, and incompletely digested antigens to enter the submucosa, activating dendritic cells, macrophages, and T cells, thereby triggering a systemic inflammatory response.[84,85] When the intestinal barrier is compromised, pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are recognized by dendritic cells and macrophages through Toll-like receptors (TLRs), activating NF-κB and MAPK

signaling pathways. This induces the excessive secretion of downstream inflammatory cytokines (TNF-α, IL-6, IL-1β), further causing esophageal and gastric mucosal damage.[86,87] Additionally, inflammation in the gut is transmitted via BGA neural signaling. The activated central HPA axis regulates immune cell activity in a bidirectional feedback loop, influencing gastrointestinal motility and gastric acid secretion. The immune-neuro mechanism also explains the clinical phenomenon of emotional disorders, such as depression and anxiety, often observed in GERD patients, creating a vicious cycle.[88] Gut microbiota regulate gastrointestinal immune responses by producing SCFAs, modulating mucus secretion, and competitively inhibiting harmful bacterial growth.[84] When dysbiosis occurs, pathogenic bacteria increase, weakening tight junctions, and increasing intestinal permeability, which in turn activates immune responses and inflammatory signaling.[89] However, current research has not yet demonstrated whether dysbiosis initiates the neuro–immune circuits by altering intestinal barrier permeability. Causal evidence from microbiota-targeted interventions is lacking, and the mechanistic role of the gut microbiota as a mediator within the neuro–endocrine–immune system remains uncertain.

In summary, the immune–inflammatory mechanisms of GERD are centered on the coordinated dysregulation of "immune cells–immune mediators–gastrointestinal barrier" and are deeply integrated into stress-induced "neuro–immune circuits". Barrier disruption leads to antigen leakage, activating antigen-presenting cells and T/B lymphocytes to initiate inflammation. Cytokines such as TNF-α, IL-6, and IL-8 not only exacerbate mucosal injury but also sensitize nerve endings, while concurrently activating the HPA axis via the BGA, with cortisol providing feedback regulation of immunity and inflammation. This establishes a closed loop of "barrier damage–immune activation–neural sensitization–central feedback–inflammation amplification", which accounts for GERD chronicity and subtype heterogeneity, and elucidates the bidirectional relationship between emotional states and inflammation.[90]

However, cell-specific targets within the "neuro–immune circuits" (eg, TLR subtypes, cytokine receptors) remain poorly characterized. With the advancement of immunotherapeutic technologies, the targeting potential of TLRs in cancer and infectious disease treatment has become increasingly evident, and TLR ligands, as key functional molecules for these targets, demonstrate substantial therapeutic promise.[91] Future studies integrating single-cell sequencing and multi-omics approaches are warranted to further elucidate mechanistic details and facilitate the translation of GERD immune–neural interventions from "mechanistic exploration" to "clinical standardization".

Conclusion

BGA is a complex, bidirectional, interactive system, encompassing neural, endocrine, and immune signaling networks, all of which contribute to the pathophysiology of GERD. In particular, the vagus nerve, HPA axis, gut microbiota, SCFAs, and serotonin have attracted increasing research attention, aiming to elucidate how the BGA contributes to the pathogenesis of GERD. As a novel paradigm, the BGA may offer new therapeutic strategies for GERD. However, Current research on GERD mechanisms still faces several unresolved core issues, necessitating further investigation. To address these knowledge gaps, future studies should focus on several key directions. First, the identification of biomarkers associated with BGA dysregulation is essential for the early and precise clinical diagnosis and assessment of GERD pathophysiology. For instance, investigations of BGA-related metabolites should focus on the relationship between "metabolites–barrier permeability–pathological effects", comparing the impact of these metabolites on intestinal and blood–brain barrier permeability under physiological versus pathological conditions. It remains to be determined whether differences in barrier permeability are associated with comorbid anxiety or depression in GERD patients, which should be further validated through clinical data analysis and animal experiments to establish a causal link between metabolite-mediated barrier disruption and GERD comorbidities.

Second, longitudinal studies are warranted to systematically assess dynamic changes in BGA dysregulation throughout the course of GERD and their relationship with symptom relief. By integrating GERD disease staging, differences in BGA characteristics at various stages should be analyzed—for example, whether early disease is primarily associated with mild gut microbiota imbalance, whereas chronic persistent stages exhibit coordinated dysregulation of the "microbiota–metabolite–barrier" axis. Such stage-specific differences may serve as potential markers for predicting GERD progression risk.

Finally, clinical trials should emphasize the evaluation of BGA-targeted interventions, such as behavioral therapy, psychological interventions, and acupuncture, to clarify their regulatory effects on the BGA and systematically validate

their clinical potential. Through further multicenter, prospective cohort studies and brain–gut axis–targeted clinical trials, the BGA is expected to provide new research insights and therapeutic breakthroughs for GERD, thereby advancing the development of personalized treatment strategies.

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Disclosure

The authors declare that there are no financial conflicts of interest or other potential conflicts of interest related to this study during the conduct of the research and the writing of this manuscript. All authors have read and approved the content of the manuscript, and there are no other relevant factors that could affect the objectivity of the research.

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