

Short title: The Gut–Brain Axis

Interrelationship Between Psychological Stress and Gastrointestinal Physiology: Role of the Gut–Brain Axis

Journal of AYUSH: Ayurveda, Yoga, Unani, Siddha and Homeopathy

ISSN: 2278-2214 (Online) ISSN: 2321-6484 (Print)

Volume 15, Issue 2, 2026

Article Type- Review

Article Received date: 05/06/2026

Article Accepted date 12/06/2026

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ABSTRACT

The relationship between stress and gut microbiome is a critical area of medical research underscoring the relativity and impact of psychological and emotional states on gastrointestinal (GI) health. This paper investigates the intricate relationship between stress and digestive health by analysing the influence of stress hormones, gut–brain interactions, and psychosocial determinants. Both acute and long-standing stress responses may disrupt normal gastrointestinal activity, affecting motility, secretion, intestinal microbiota, and overall digestive well-being, often leading to gastrointestinal disorders such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD). Stress regulation within the body involves major neuroendocrine pathways, particularly the hypothalamic–pituitary–adrenal axis and the autonomic nervous system, both of which can alter normal digestive functioning. The gut and the brain communicate through interconnected neural and biochemical pathways involving both the central and enteric nervous systems. In addition, emotional and social influences such as anxiety, depression, and chronic life stress may aggravate gastrointestinal discomfort and negatively affect digestive health. By delving into contemporary research findings and the underlying biological mechanisms, this paper provides a refined understanding of how stress influences digestive function and how digestive health, in turn, affects psychological well-being. The insights gained aim to inform more holistic approaches to managing and treating stress-related gastrointestinal disorders. Through profound comprehension, clinicians and researchers can pave the way for more precise, targeted

interventions to alleviate the stress-linked gastrointestinal disorders and amplify the health status ubiquitously.

Key words: Gut, brain, microbiome, stress, hypothalamus-pituitary-adrenal axis

INTRODUCTION

The relationship between stress and digestion explains how mental and emotional stress can affect the normal functioning of the gastrointestinal (GI) system and overall digestive health. Psychological stress and digestive physiology continuously influence each other through multiple biological pathways, with each exerting significant influences on the other through a complex web of physiological, psychological, and behavioural pathways. While stress is often perceived as a purely psychological phenomenon, its impact extends far beyond the realms of the mind, profoundly affecting various bodily systems, including the digestive system. Similarly, digestive health can also affect stress levels and a person's overall well-being[1].

The digestive system, responsible for the breakdown of food, nutrient absorption, and waste elimination, is highly sensitive to emotional and psychological states. Stress, encompassing emotional, psychological, and physical strains, can significantly impact digestive functions, leading to various gastrointestinal disorders. A clear understanding of these interconnected mechanisms is important for the development of successful prevention methods and treatment strategies for gastrointestinal conditions influenced by stress. Coeval studies reveal that stress influences digestion through myriad mechanisms, including the release of stress hormones, alterations in gut-brain communication, and changes in gut microbiota[2].

MATERIALS AND METHODS:

The present study included reviews on the gut-brain axis based on various articles. The collected information explains how two-way communication between the gut microbiome and the central nervous system affects mental health, cognitive function, and behaviour.

LITERATURE REVIEW

Communication between the gastrointestinal tract and the brain is coordinated through an extensive network involving both the central and peripheral nervous systems. The brain functions as the principal regulatory organ responsible for processing sensory information, controlling motor activity, and coordinating emotional and cognitive responses. Anatomically, it consists of the cerebrum, diencephalon, brainstem, and cerebellum, each contributing distinct physiological functions. The spinal cord serves as a major conduit for neural transmission between the brain and peripheral tissues while also mediating reflex activity. Together, these

structures integrate internal and external signals, allowing the body to maintain homeostasis and respond appropriately to environmental and physiological changes[3].

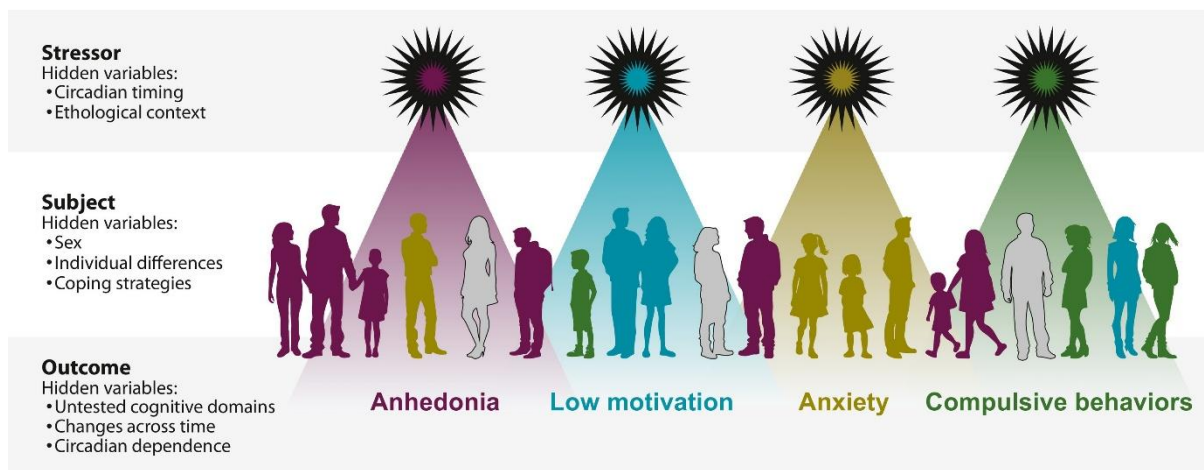
Recognition of the association between emotional health and gastrointestinal function has existed for many decades. Early observations suggested that psychological disturbances could influence digestive processes, leading researchers to investigate the biological links between the brain and the gastrointestinal tract. Subsequent studies demonstrated that alterations in mood, stress, and anxiety may influence gut physiology and microbial composition, thereby contributing to inflammatory responses and changes in intestinal barrier function[4].

Hypothalamic–Pituitary–Adrenal (HPA) Axis:

Physiological adaptation to stress involves coordinated neuroendocrine mechanisms, among which the hypothalamic–pituitary–adrenal (HPA) axis is particularly important. Through hormonal signalling, this system influences numerous biological functions including immune regulation, metabolism, emotional responses, and gastrointestinal activity. The hypothalamus, pituitary gland, and adrenal glands function together to generate an integrated stress response. Because of its close interaction with neural pathways connecting the gut and brain, activation of the HPA axis can significantly modify digestive physiology during stressful conditions[5].

Stress:

Stress is a subjective psychophysiological phenomenon that cannot be directly quantified through objective physical parameters⁴. Nevertheless, its presence can be indirectly evaluated through associated clinical manifestations such as fatigue, insomnia, elevated blood pressure, exhaustion, and reduced functional capacity. Physiologically, stress represents an adaptive biological response initiated to counteract internal or external stressors and to preserve homeostasis. However, when stress becomes persistent or recurrent, it may transition into a pathological state characterized by anxiety, depressive symptoms, irritability, and restlessness¹. The overall impact of stress is largely determined by its duration and intensity; acute stress associated with anticipated challenges may enhance adaptive performance, whereas episodic acute stress and chronic stress exposure are linked to detrimental health consequences[6]. (Figure 1).



Trends in Neurosciences

Figure 1: Trends in Neuroscience.

Stress and the Hypothalamus-Pituitary-Adrenal (HPA) axis

Gastrointestinal function is regulated through complex interactions between neural, endocrine, immune, and microbial systems. Signals originating from the digestive tract can influence central nervous system activity, while psychological stress can modify gastrointestinal motility, secretion, sensitivity, and microbial balance. Activation of the sympathetic nervous system and the HPA axis promotes the release of catecholamines and glucocorticoids that facilitate adaptation to stressful situations. However, prolonged exposure to these mediators may impair immune regulation, disrupt intestinal barrier integrity, and contribute to chronic inflammatory processes within the gastrointestinal tract [7](Figure 2).

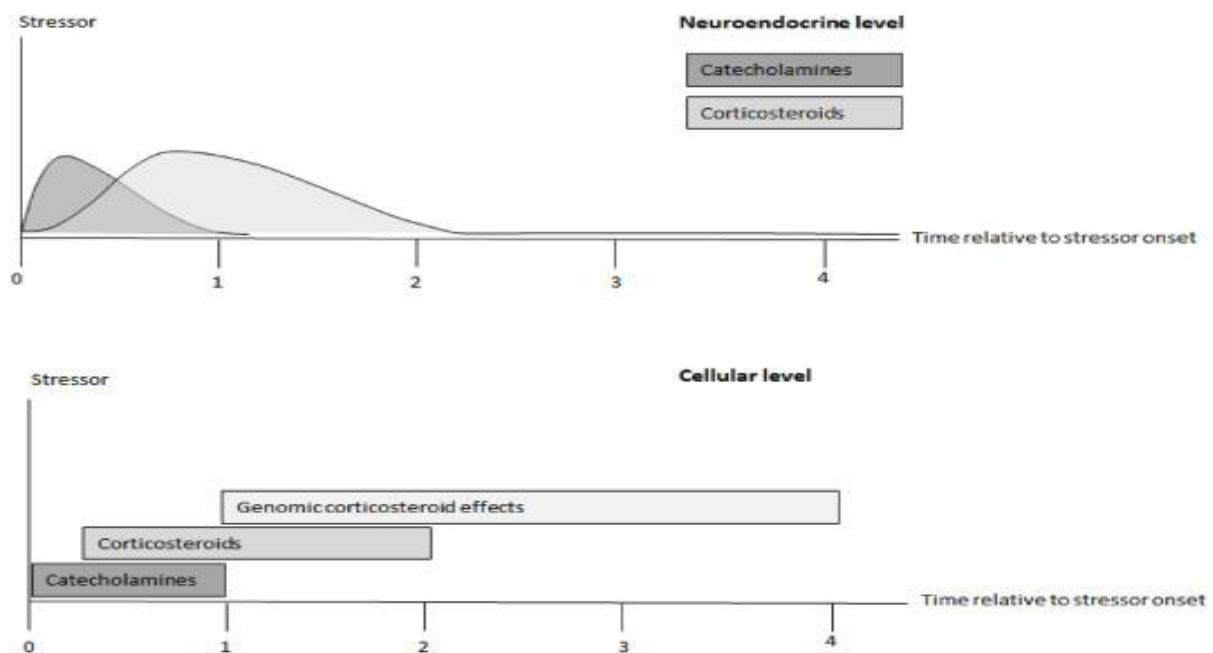


Figure 2: Neuroendocrine and cellular responses to a stressor over time

Stress at cellular level and gut microbiome:

Oxidative stress is a key factor influencing physiological balance within the gastrointestinal system. It arises from both internal metabolic processes and external environmental exposures, contributing to cellular strain. A wide variety of microorganisms residing within the gastrointestinal tract contribute significantly to immune modulation and the maintenance of internal physiological stability. However, exposure to psychological and chemical stressors can disturb this balance, leading to localized oxidative damage and weakening of the intestinal barrier[8].

At the cellular level, injury to mitochondrial DNA in intestinal epithelial cells increases the production of reactive oxygen species (ROS), intensifying oxidative damage. Biomarkers such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) are associated with mitochondrial dysfunction and may trigger programmed cell death. As barrier integrity declines, microbial components can cross into systemic circulation, activating immune responses. For instance, lipopolysaccharides (LPS) interact with TLR-4 receptors, initiating inflammatory signalling cascades[4].

As a result, increased generation of inflammatory cytokines and reactive nitrogen molecules may occur, leading to further progression of tissue and cellular damage. Activation of pathways such as NF- κ B and enzymes like NADPH oxidase amplifies inflammation. While certain gut microbes contribute to oxidative stress, others produce metabolites with antioxidant properties, highlighting the importance of maintaining redox equilibrium for intestinal and systemic health [5].

Vago-vagal reflex :

Bidirectional communication between the gut and the brain is partly mediated through vagal neural pathways. Sensory information arising from the gastrointestinal tract is transmitted to central processing centres, where it is integrated and subsequently relayed back to the digestive system through efferent signals. This mechanism contributes to the regulation of digestion, appetite, immune activity, and visceral function. Neurotransmitters and gastrointestinal hormones participate in this communication network, enabling coordinated responses that help maintain physiological balance[9].

Gut-brain axis and food consumption:

Psychological and physiological factors interact closely in the development of psychosomatic conditions. The hypothalamus serves as a central regulatory structure that integrates neural and endocrine signals involved in maintaining energy balance and homeostasis. Following food intake, gastrointestinal hormones communicate satiety-related information to the brain through neural and hormonal pathways[5]. Exposure to chronic stress may disrupt these regulatory mechanisms, altering appetite control, food preferences, and metabolic processes. Such changes can promote unhealthy dietary behaviours and increase susceptibility to metabolic and stress-related disorders[7].

DISCUSSION:

The gut and brain are interconnected through a complex bidirectional communication network known as the gut–brain axis. This when necessitated acts in association with the endocrine system especially the hypothalamus, and affects the pathophysiological states of the body in response to stress. Owing to its important function in the gut–brain connection, the vagus nerve has become a major focus of scientific research. The vago-vagal pathway innervates the sensory endings of the vagus nerve located in the GI tract to the periventricular nucleus of the hypothalamus [10]. There is substantial evidence that this controls satiety, and homeostasis. The feedback mechanism linked through the Hypothalamus-Pituitary-Adrenal (HPA) axis checks on the hormones [8]. An individual is not diagnosed with psychiatric disorders solely on the basis of stressors experienced; rather, diagnosis is based on the clinical manifestations and associated functional impairment. The stress occurring at the neural level can be coarsely linked with the gut[8]. Persistent and poorly regulated stress can significantly influence dietary habits, often increasing the preference for and intake of highly palatable foods rich in sugar and fat. With prolonged exposure, such stress may elevate allostatic burden and produce neurobiological modifications that encourage repetitive and compulsive behavioural patterns. From a neuroendocrine perspective, long-term stress can alter the functioning of the mesolimbic dopaminergic pathway along with other brain regions associated with stress regulation. Collectively, these alterations may enhance reward responsiveness, intensify cravings and food-seeking behaviour toward hyperpalatable foods, and contribute to metabolic disturbances that favor increased body weight and adipose tissue accumulation [9].

The gut–brain axis represents an integrated communication network involving neural, endocrine, immune, and metabolic pathways that connect the gastrointestinal tract with the central nervous system. Current evidence indicates that intestinal microorganisms contribute

significantly to this interaction by influencing immune responses, neurochemical signalling, and physiological regulation[9]. Disturbances in microbial balance may affect gastrointestinal function as well as psychological well-being, highlighting the importance of maintaining a stable microbial environment for overall health.

In conditions such as irritable bowel syndrome (IBS), alterations in microbial composition stimulate mucosal innate immune responses, leading to increased intestinal epithelial permeability, activation of visceral pain pathways, and dysregulation of the enteric nervous system. Large population-based studies have demonstrated a strong association between anxiety, depression, and functional gastrointestinal disorders, challenging earlier assumptions that psychological comorbidities observed in clinical settings were merely the result of health-seeking behaviour driven by neurotic tendencies.

Information exchange between the gut and the brain occurs through several interconnected pathways. Neural signals, endocrine mediators, immune responses, and microbial metabolites collectively influence physiological processes in both systems[10]. Gut-derived bioactive compounds can affect brain function, while central nervous system activity may alter gastrointestinal physiology. These interactions demonstrate the dynamic and reciprocal nature of gut–brain communication.

Many gastrointestinal disorders are associated with altered signalling along the gut–brain axis, shaped by both genetic predisposition and environmental influences. The microbiota–gut–brain axis encompasses microbial metabolites, the enteric nervous system, autonomic nervous system components (both sympathetic and parasympathetic), neuroimmune interactions, neuroendocrine pathways, and the central nervous system. The exchange of signals between the gastrointestinal tract and the brain occurs through integrated pathways involving neural communication, HPA axis–mediated endocrine responses, immune system interactions, microbial production of neuroactive compounds, and physiological barriers including the intestinal lining and the blood–brain barrier. These coordinated processes collectively reflect the dynamic two-way relationship between stress and the gut–brain axis.

CONCLUSION

The relationship between the gut microbiome and the brain is a complex two-way communication system between the enteric nervous system (ENS) and the central nervous system (CNS). Stress can disturb the gut and its microbiota, which may negatively affect overall health. Gut microbiota also plays an important role in psychosomatic responses. Increased activity of the sympathetic nervous system and the hypothalamic–pituitary–adrenal (HPA) axis, along with higher cortisol levels, can lead to prolonged stress, inflammation, and changes in neurotransmitter metabolism. Therefore, the gut–brain axis plays an important role in connecting the emotional and cognitive functions of the brain with the gut.

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