THE GUT BRAIN AXIS: EFFECT OF THE GASTROINTESTINAL TRACT ON MENTAL AND OVERALL HEALTH

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**ABSTRACT**

The gut-brain axis is a bidirectional communication network linking the gastrointestinal tract and the central nervous system via neuronal, hormonal, and antibody signaling pathways. Emerging evidence suggests that the composition and activity of the gut microbiota play a crucial role in influencing brain function and may contribute to the development and progression of various mental disorders. This review highlight the association between gut health and cognitive functioning and the mechanisms by which gut microbiota influence brain health.

**INTRODUCTION**

The gut-brain axis is a communication pathway that allows a two-way exchange of information between the microbiota of the gastrointestinal tract and the nervous system of humans. The vagus nerve, which is responsible for facilitating communication, provides support for this axis.The gut had always been considered a digestive organ until the discovery of the gut–brain axis. The gut–brain axis is a connection through which the microbes within the gut are able to influence and control the emotions as well as the cognition of an individual through neuro-immunoendocrinological pathways (Chang *et al, 2022)*.

 This review highlights some of the well-established discoveries of the gut–brain axis, explaining the mechanism of action on how gut microbes modulate the formation of the enteric nervous system and the production of neurohormones and chemokines to alter the cognitive performance of the brain and the emotional balance of an individual through neural, immune and endocrine pathways. Moreover, the gut-brain axis acts as a new key to understanding the mind–body connection.

The enteric nervous system had been regarded as a digestive organ until the remarkable discovery made by Michael Gershon that 90% of the body’s serotonin is located within the walls of the gastrointestinal (GI) tract (Han *et a*l,2019). This ignited the interest of various neuroscientists, including psychiatrists, regarding the GI nervous system. The enteric nervous system is composed of neuronal plexuses (e.g. Meissner’s plexus and Auerbach’s plexus), surrounded by a pool of more than 30 neurotransmitters (e.g. serotonin, dopamine, glutamate, noradrenaline and nitric oxide) and other chemical mediators (e.g. neuropeptides and enkephalins). It also contains glia-like supportive cells, and together contains nearly 100 million neurons, similar to the number of neurons in the spinal cord (Liu *et al*. 2019 ; Muddsar *et al*., 2024).

The gut–brain axis describes the bidirectional neural pathways linking cognitive and emotional centres in the brain to the neuroendocrine centres, the enteric nervous system and the immune system. Emotional states, such as depression, and behavioural dispositions, ranging from hostility to psychosocial stress, can directly influence both physiological function and health outcomes in different ways; (Anton and Cortizo, 2005) one such example is the gut–brain connection. The gut–brain connection is intimately involved in explaining how inflammatory response induced by psychosocial stress in the gut is modulated by bidirectional communication between the neuroendocrine and immune system of the gut with brain. Many areas of research have established multiple pathways by which the immune system and the enteric nervous system communicate bidirectionally with the brain. (Zheng *et al* ,2029; Natasha *et al*., 2023).

 There are two types of gut flora. Normal gut flora is essential to maintain the gut–brain axis, thereby ensuring a good mood is maintained; the composition of normal gut flora varies from person to person. In addition, there is also variation based on the location of the gut microbes in the gut of different individuals. As a result of this variation, there is a diverse pattern of the enteric nervous system which differs between individuals, as these microbes are essential for the production of serotonin. Serotonin is vital for the development and maturation of the enteric nervous system in order to maintain a homeostatic gut–brain axis. Any disruption in the growth of normal microbes impairs cognitive and emotional balance (Stasi et al., 2019; McGovern et al., 2019) whenever the gut is exposed to pathogenic microbes; secretory immunoglobulin A (IgA) is constantly produced (60mg/kg) at the interface between GI mucus and lumen by plasma cells to prevent adhesion of these pathogens, thus maintaining a homeostatic gut–brain axis(Bharwani *et al*., 2020). When an individual is under stress, IgA production decreases, leading to activation of proinflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukins 1, 6 and 8, which spontaneously stimulate the hypothalamus to produce corticotropin-releasing hormone (CRH) by two routes:

 (1) crossing the blood–brain barrier via the bloodstream and

(2) the vagus nerve, which carries 90% of information of immune status from the periphery to the central nervous system (CNS)(Bharwani *et al*., 2020) .

Thus, CRH in turn stimulates adrenocorticotropic hormone from the anterior pituitary to produce cortisol from the adrenal cortex (Watkins and Maier, 1999). Under stress, TNF-α upregulates indoleamine 2,3-dioxygenase, a catabolic enzyme that degrades tryptophan in order to prevent bioavailability of tryptophan for microbes; serotonin formed from tryptophan is vital for elevation of mood and its deficiency leads to depression. Furthermore, the released cortisol stimulates tryptophan-2,3-dioxygenase to produce kynurenine, which further forms neurotoxic quinolinic acid (a N-methyl-D-aspartate receptor agonist), thereby impairing cognition.(Kiank et al., 2010, Hameed *et al*, 2024). The enteric nervous system communicates with the CNS through neural, immune and endocrine pathways, which may help in understanding the mind–body connection. (Fahad et al 2016)

**The Gut-Brain Axis (GBA)** is a communication system between the digestive tractand the brain. This pathway is bidirectional, meaning the brain communicates with the gut, and the gut also communicates information to the brain. It is a two-way communication between central nervous system (CNS) and enteric nervous system (ENS), linking emotional and cognitive centers of the brain with peripheral intestinal functions. The gut microbiota plays a very important role in the gut-brain axis (GBA). The human body is a super-complex ecosystem containing trillions of bacteria and other microorganism, which inhabit skin, mouth, sexual organs, and intestines. These commensals and microorganisms are vital for maintaining body homeostasis and may also be involved in the etiology of several metabolic, immune and mental disorders. This bidirectional interaction between microbiota and brain appears to be by means of a complex neural, endocrine, immune, and humoral network. In clinical practice, evidence of microbiota and brain interactions comes from the association of gut dysbiosis (an imbalance of microbial species and a reduction in microbial diversity within certain bodily microbiomes (i.e., the collection of microorganisms existing in a specific part of the human body) with central nervous disorders (e.g., autism, anxiety-depressive behaviors) and functional gastrointestinal (GI) disorders like irritable bowel syndrome (IBS)

The ENS as a distinct entity was postulated initially and then through animal experiments, it was revealed that even when the gut is completely denervated from CNS, it can function by itself. The ENS has about 100 million neurons and is a part of CNS that is separated during development; however, it retains a two-way communication pathway with the CNS. Gut is controlled by the autonomic nervous system (ANS) consisting of parasympathetic and sympathetic systems, and also by the local enteric nervous system consisting of the myenteric (Auerbach plexus) and Meissner’s (submucosal plexus). Parasympathetic control of the CNS is through vagal nerve with efferent cholinergics acting on the myenteric plexus (motor movements) and Meissner plexus (submucosal glands secretions). The sympathetic control is through the splanchnic nerves which decrease motility of gut and blood supply of splanchnic circulation.



CNS, central nervous system.

FIG. 1: Neural substrates of gut-brain axis (GBA).(Jagielski, 2021)

The GBA involves communication between several systems in the body:

**Nervous System** – Playing a role in nearly every aspect of our health, the nervous system is involved in automatic activities such as breathing, and in complex processes such as thinking, reading, remembering, and feeling emotions.

 **Endocrine System** – Consisting of all the body's different hormones, the endocrine system regulates all biological processes in the body.

**Immune System** – This network of biological processes protects the body from diseases. The GBA also communicates with the *gut microbiome*, which includes all the bacteria in the intestines. .

**The role of the nervous system**:

**The Autonomic Nervous System (ANS)** is responsible for bodily functions that are not consciously controlled. This includes a person’s blood pressure, heart rate, respiratory rate, and digestion. The ANS is divided into the sympathetic and parasympathetic (vagal) nervous system.The sympathetic nervous system (SNS)is associated with the “fight, flight, or freeze” response, also known as the “stress” response. It is often compared to the gas pedal of a car: when the brain detects a stressful event, the SNS sends signals to the body by releasing adrenaline from the adrenal glands. This can cause increased heart rate and blood pressure, rapid breathing for increased oxygen intake (to increase alertness) and release of glucose to supply additional energy. While energy is being directed to the heart, lungs, muscle, and brain during the sympathetic response, blood flow is directed away from the digestive tract, leading to delayed digestion and decreased oxygen to the GI tract. This can result in abdominal symptoms such as indigestion or nausea. The stress response can also result in stimulation of the large bowel, which may contribute to increased need to have a bowel movement (also known as *urgency).*

The parasympathetic (vagal) nervous system (PSNS):While the SNS response works like a gas pedal, the parasympathetic response acts like a brake. Known as the “rest-and-digest process,” the PSNS helps the body recover the energy expended during stressful periods and promotes relaxation and healthy digestion. The vagal nerves that communicate between the brain and gut are part of the PSNS.

Heart rate, blood pressure, and breathing patterns return to healthy levels, muscles relax, and the blood flow and oxygen are returned to the digestive tract. Production of saliva resumes, as does the release of digestive enzymes, and motility increases.

**The endocrine system**: The *hypothalamic-pituitaryadrenal axis (HPA axis)* is the neuroendocrine systeminvolved in the response to stress. The hypothalamusand pituitary glands are located in the brain, and theadrenal glands are located on top of the kidneys. Thehypothalamus, pituitary glands, and adrenal glandsinteract by releasing stress hormones. The adrenal glandreleases cortisol*,* which has a fluctuating, cyclical pattern.Higher amounts of cortisol are typically released uponawakening to supply energy, but this level decreasesthroughout the day. When a person experiencesincreased stress, higher cortisol levels can provide theenergy needed to respond to the crisis. Cortisol levelsreturn to normal after the stressor resolves. However,chronic stress can result in improper function of the HPAaxis and has been associated with poorer mental health,increased inflammation, sleep disorders, metabolicproblems, and GI conditions.

GUT-BRAIN SIGNALING

There are four main signaling pathways in the GBA, the neural pathway, enteroendocrine signaling, serotonin and tryptophan pathway and finally immune signaling (Mertz, 2003)



FIG. 1: Gut-brain axis signaling pathways.

GABA, gamma-aminobutyric acid; SCFA, short-chain fatty acid; PYY, peptide YY; CCK, cholecystokinin; IL, interleukin;

GLP-1, glucagon-like peptide 1; TNF, tumor necrosis factor.

**The Body’s Second Brain:** Information received from the brain and spinal cord, the autonomic nervous system (ANS), immune system, and endocrine system all come together in what is known as the Enteric Nervous System (ENS)–a large and complex system that organizes gastrointestinal (GI) activity. Infact, while the ENS receives input from the brain or spinal cord, it can function independently, leading some healthcare providers to refer to it as the body’s “second brain.” The ENS contains more than 100 million nerve cells lining the digestive tract from mouth to rectum. Neurotransmitters or neurochemicals such as serotonin (a mood stabilizer) and dopamine (involved in pleasurable experiences) are responsible for communication between the brain and the gut. In fact, the gut contains greater than 90% of the body’s serotonin and half of the body’s dopamine. The large presence of these neurotransmitters in the digestive tract and the brain play a significant role in the use of certain medications that work as neuromodulators.

**Neural Pathways**: Central nervous system control over the ENS is important for adaptive gut responses during stressful events that signal homeostatic threat to the organism. Vagal nerve transmits signals from gut microbiota like Lactobacillus rhamnosus which alters central gamma-aminobutyric acid (GABA) receptor expression and results in reduced anxiety and depressive behavior (Bravo et al., 2011) In a colitis model, Bifidobacterium longum caused an anxiolytic effect again through an intact vagus nerve (Bercik et al., 2011).

**Enteroendocrine Signaling:**The bacterial byproducts on coming in contact with the gut epithelium stimulate enteroendocrine cells to secrete neuropeptides. These peptides diffuse throughout the lamina propria to produce local effects on intrinsic ENS, and also enter the bloodstream to act on CNS (Kunze et al., 2009). Various neuropeptides involved in enteroendocrine signaling are peptide YY (PYY), neuropeptide Y (NPY), glucagon-like peptide (GLP 1 and 2) and substance P (Cani et al., 2013) Serotonin and Tryptophan Pathway Serotonin (5-HT) is an important neurotransmitter within the brain and ENS. About 95% of 5-HT in the body is produced by gut mucosal enterochromaffin cells and ENS neurons (Yano et al ., 2015) Peripherally, 5-HT is involved in the regulation of GI secretion, motility (smooth muscle contraction and relaxation), and pain perception. In brain 5-HT signaling pathways are implicated in regulating mood and cognition. Spore-forming bacteria in the gut promote 5-HT biosynthesis from colonic enterochromaffin cells and seem to play a role in GI disorders (IBD) and mood disorders (depression) (Bilbo, et al., 2012).

**Immune Signaling:** Gut-associated lymphoid tissues form the largest immune organ of the human body, and it comprises more than 70% of the total immune system. It provides a vital defensive barrier between externally-derived pathogens and the internal biological environment. Infectious microorganisms cause behavioral problems through activation of the immune pathways in the gut that influence the brain. C. jejuni administration to mice at subclinical doses results in anxiety like behavior (Bilbo and Schwarz, 2012). Microbiota metabolites upregulate T regulatory cells synthesis and secretion of the anti-inflammatory cytokine, IL-10. Oral consumption of Bifidobacterium infantis in humans is associated with enhanced IL-10 expression in peripheral blood (Dinan and Cryan, 2013). Therefore, the balance of gut microbes may closely regulate host inflammatory responses.

**GUT MICROBIOTA:** The term “microbiota” refers to an ecological community of commensals, symbiotic and pathogenic microorganisms that literally share our body space. Friedrich Escherich first cultured Escherichia coli from healthy people and Joshua Lederberg suggested the term microbiota. There exists a symbiotic relationship between the host organisms and the microbiota which are co-dependent on each other for survival. Total microbial cells in the gut are actually more than the human cells in the body. Total weight of these gut microbes is 1–2 kg (similar to the weight of the human brain) (Stilling et al., 2014). Cumulative number of genes in the pool of microorganism in the gut is larger than that in the human genome. The gut has about 100 trillions of microbes— bacteria, yeasts, helminthes, viruses, and protozoa. The phylogenetic composition of the microbiota in various parts of the gut is as shown in the diagram below

 

FIG. 2: Composition of the gut microbiome

FFAs, free fatty acids; SCFAs, short-chain fatty acids.

The colonization of the gut microbiota commences at birth and the factors deciding microbiota composition include, mode of delivery, breastfeeding, infection, antibiotics, diet and stress.(Donnet-Hughes et al., 2010)

**ROLE OF GUT-BRAIN AXIS IN HEALTH**

Bacterial colonization of the gut is central to development and maturation of both ENS and CNS. Absence of microbial colonization results in altered gene expression and turnover of neurotransmitters in CNS and ENS. It also causes alterations of gut sensory-motor functions and delayed gastric emptying and intestinal transit(Barbara et al., 2005). Lactobacilli generate nitric oxide and hydrogen sulfide that modulates gut motility by interacting with vanilloid receptors in the gut mucosa (Stilling et al., 2014). Microbiota influences stress reactivity and anxiety-like behaviour by regulating the set point of hypothalamicpituitary axis (HPA). They also modulate the serotonergic pathways in the limbic system (Clarke et al., 2013). The micrbiome influences

gut motility by maintenance of the mucous layer and biofilm through secretion of various acids, bicarbonates and mucus. This helps in intestinal fluid handling and in mucosal immune responses (Husebye et al., 2001).

**Gut-Brain Dysfunction**

When the Gut-Brain Axis (GBA) is out of balance, normal sensations—such as food moving through the digestive tract—that would typically not be noticed or considered bothersome, can be experienced as unpleasant symptoms. In other words, the gut can be more sensitive than normal. A number of factors that can influence Gut- Brain dysfunction:

• *Stress* – As noted above, stressful events, as well as long-lasting or recurring stress, can lead to dysregulation of the Gut- Brain Axis, including activation of the autonomic nervous system (ANS) and hypothalamic-pituitaryadrenal axis (HPA axis), which can worsen GI symptoms. Stress can also result in changes in gut motility and permeability. (Jakielski et al., 2021).

ROLE OF GUT-BRAIN AXIS IN DISEASE

Role of microbiota in disease was noticed several years back when gut antibiotics were given for hepatic encephalopathy. Role of microbiota is rapidly emerging in gut-brain communication and alterations in the composition of gut microbiota have been observed in several diseases as illustrated below:



Fig 3. Disorders associated with impaired gut-brain axis (GBA).

IBS, irritable bowel syndrome.

Depression

Major alteration in the gut population of Acinetobacter and Bacteroides has been observed in patients with depression. Mice receiving microbiota from patients with depression, developed depressive behavior and disturbances in hippocampal gene activation (Kelly et al., 2016). Depressed patients have abnormal immune system and brain anomalies resulting in decreased levels of 5-HT and brain-derived neurotrophic factor along with changes in neuronal morphology in the amygdale. Microbial metabolites like short-chain fatty acids, butyrate, propionate and acetate are key products of the gut microbiota. Increased acetate by altered gut microbiota results in activation of the parasympathetic nervous system. This increases glucose-stimulated insulin and ghrelin secretion causing hyperphagia, obesity and related sequelae associated with depression (Luna *et al* 2015).

By elucidating the influence of the gut microbiota and the interaction between antidepressants and the gut-brain axis, it may be possible to improve the availability of treatment options and preventive measures for individuals with major depressive disorder (MDD). Recent advances in the treatment of MDD have placed gut microbiota in the limelight, emphasizing its significance as an area of investigation (Siopi et al., 2020). By examining the effect of changes in gut microbiota on the efficacy of selective serotonin reuptake inhibitors (SSRIs) on the gut-brain axis, we

can gain important insights into the treatment of depression and MDD.

Emerging evidence suggests that gut microbiota and epigenetics can directly influence the pathogenesis of AD via their effects on multiple pathways, including neuroinflammation, oxidative stress, and amyloid protein( Priyanka *et al,*2021).

The gut microbiota imbalance has been proven in animal studies to affect brain chemistry, metabolic status and neuronal function . Short Chain Fatty Acids(SCFAs ) can cross the blood–brain barrier (BBB) via monocarboxylate transporters (MCTs) by overexpressing tight junction proteins and maintaining the integrity of the BBB . SCFAs such as propionate, butyrate and acetate may modulate the levels of neurotrophic factors (BDNF), promote neurogenesis, influence glial cell morphology and function, contribute to serotonin formation and improve neuronal homeostasis and function, all of which help to regulate neuroinflammation in the CNS . The engagement of SCFAs with these gut–brain networks can alter cognition, emotion and the pathophysiology of mental disorders directly or indirectly . Changes in neurotransmitter activity via modulatory pathways including the kynurenine pathway (Silva *et al,*2020).

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