Gut–brain axis: Synergistic approach

ABSTRACT
Since decades, there is a change in concept of the gut–brain axis. There is differential increase in evidences focusing on the bidirectional communication between the gut microbiome and the brain. It supports existence of far-reaching model of “gut–brain axis.” This axis is attaining more adherence to fields investigating biological and physiological footing of psychiatric, neuro-developmental, age-related, and neurodegenerative disorders. Many factors can change microbiota composition in early life as well as with the increasing age. Stress can affect the microbiota–gut–brain axis at every stages of life. Recent advances have involved the gut microbiota in many conditions including severe mental illness, autism, anxiety, obesity, Parkinson’s disease, and Alzheimer’s disease. The current studies target on elaborating the underlying mechanisms of microbiota–gut–brain axis and attempt to exemplify intervention and therapeutic strategies for neuropsychiatric disorders.

Keywords: Enteric nervous system, gut–brain axis, microbiota, psychiatric disorder

It was proposed 2000 years back by the Greek physician Hippocrates that “all diseases begin in the gut.”[1] Interest in this field was sparked when a study in 2004 showed that germ-free (GF) mice showed an exaggerated hypothalamic–pituitary–adrenal (HPA) axis response to stress compared to non-GF laboratory mice.[2]

GUT MICROBIOTA
Gut microbiota is an ecological community of commensals, symbiotic, and pathogenic microorganisms. It helps to collaborate dynamic metabolic ecological balance. About 80% of bacteria of all the estimated adult’s body are present in gut, about nine-ten times as many as cells in comparison to the human body. The gut microbiome complex encodes 150 times as many genes as the human genome.[3] The microbiome is composed of two bacterial phylotypes, Bacteroidetes and Firmicutes and the smaller composition of Proteobacteria, Actinomyces, Fusobacterium, and Verrucomicrobia.[3]

Across human lifespan, diverse changes in microbial diversity are accompanied by typical changes in neural development, suggestive of ongoing neuronal processes at specific stages of life.[4]

FUNCTIONAL NEUROANATOMY
In animal model, enteric nervous system (ENS) is a distinct entity, and even when the gut is completely denervated from central nervous system (CNS), it can function by itself. The ENS 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 ENS consisting of the myenteric (Auerbach plexus) and Meissner’s (submucosal plexus). Parasympathetic control of the CNS is through vagal nerve with effenter cholinergic acting on the myenteric plexus (motor movements) and Meissner’s plexus (submucosal glands secretions). The sympathetic control is through the splanchnic nerves which decrease motility of gut and blood supply of splanchnic circulation.[9]

**GUT–BRAIN SIGNALING**

The gut microbiota communicates with the gut connectome, the network of interacting cell types in the gut that includes neuronal, glial, endocrine, and immune cells, through microbial metabolites, while changes in gut function can modulate gut microbial behavior. The brain connectome, the multiple interconnected structural networks of the CNS generate and regulate ANS influences that alter gut microbial composition and function indirectly by modulating the microbial environment in the gut.[6] Alterations in the gain of these bidirectional interactions in response to perturbations such as psychosocial or gut-directed (e.g., diet, medication, infection) stress can alter the stability and behavior of this system, manifesting as brain–gut disorders. Different two-way signaling pathways are as follows:[7]

**Neural pathways**

There are afferent spinal and vagal sensory neurons, which provide feedback from intestinal to brain stem. These descending projections from the limbic system (stress) influence autonomic activity of the gut. Signals from gut microbiota like Lactobacillus alter central gamma-aminobutyric acid (GABA) receptor expression. In a colitis model, *Bifidobacterium longum* caused an anxiolytic effect again through an intact vagus nerve.[9]

**Neuroendocrine signaling**

Stimulation of enteric neurons secretes neuropeptides, which enter the bloodstream and/or directly influence the ENS.[8]

**Serotonin and tryptophan pathway**

Serotonin (5-HT) is produced by gut mucosal enterochromaffin cells (95%). The peripheral serotonin helps in the regulation of gastrointestinal (GI) secretion, motility (smooth muscle contraction and relaxation), and pain perception. Brain serotonin is also implicated in regulating mood and cognition.[8]

**Immune signaling**

Gut-associated lymphoid tissue is the largest immune organ (70%) and acts as defensive barrier. 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.[9]

**Production of microbial metabolites**

Lactobacillus and *Bifidobacterium* secrete GABA. *Candida, Escherichia*, and *Enterococcus* secrete serotonin as their metabolite. *Bacillus* species secretes dopamine which may influence the brain connectome. Gut bacteria also produce short-chain fatty acids (SCFAs) that stimulate sympathetic nervous system, mucosal serotonin release and influence the memory and learning process in the brain.[9]

**Altered intestinal permeability**

Chronic stress leads to alteration in intestinal permeability (leaky gut syndrome) and is associated with a low-grade inflammation. Lipopolysaccharides lead to increased presence of circulating bacterial endotoxins and increases fundamental risk factors for disease.[9]

**GUT–BRAIN AXIS IN HEALTH**

Bacterial colonization in gut is central to maturation and development of both ENS and CNS. The 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. The microbiome 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.[4,5]

**GUT–BRAIN AXIS IN DISORDER**

Role of microbiota is rapidly emerging in gut–brain communication, and alterations in the composition of gut microbiota have been observed in several diseases.[9]

**GBA and depressive disorder**

Most of studies have been carried out using animal models, either by adding pathogenic bacteria and monitoring behavior or by inducing depression-like symptoms and rescuing these animals through treatment. One study showed that rats that had undergone maternal separation (model of induced depression-like behavior) could be rescued by treatment with the probiotic *Bifidobacterium infantis* in conjunction with 30 mg/kg citalopram. Maternal
separation causes reduced mobility, increased peripheral pro-inflammatory interleukin-6 secretion, and reduced levels of norepinephrine in these rats. However, these symptoms were reversed after treatment with both the probiotic and citalopram but not when they were administered separately. Functional magnetic resonance imaging (MRI) analysis has previously shown that there is a chronic low-level inflammatory condition in many cases of depression.\[11\]

**GBA and anxiety disorder**
Exposure to stress can provoke anxiety responses involving activation of the HPA axis or the immune response. Studies have also documented the coexistence of anxiety and intestinal dysfunction. Dysbiosis can induce and exacerbate anxiety through immunologic and metabolic pathways suggesting that change in gut microbiota influences the anxiety. Experimental studies indicate that probiotics may ameliorate anxiety.\[9\]

**GBA and autism spectrum disorder**
GI symptoms, feeding difficulties, are very common and usually proportional to severity of autism spectrum disorder (ASD). Increased levels of Ruminococcus and Bacteroides and decreased levels of Firmicutes have been associated with ASD. Stool samples of children with ASD show low levels of SCFAs. Probiotics and gluten-free diet modulate the gut microbiota composition and improve intestinal immune system, resulting in better symptom control.\[11\]

**GBA and Parkinson’s disease**
Different GI symptoms are present that contribute more detrimentally to quality of life of patient. Among GI symptoms, constipation is among the earliest features which appear before motor dysfunction related to dysfunctional autonomic and ENSs, such as slow-transit constipation and sensory alterations. However, relation remains limited between Parkinson's and the gut microbiota to characterizing differences against healthy controls.\[10\]

**GBA and schizophrenia**
Subjects with schizophrenia show increase levels of lactic acid bacteria and *Streptococci* species, associated with alterations in adaptive Th2 immune responses. Administration of probiotics altered the microbiome and appeared to normalize some behavioral symptoms. Clostridium produces microbial metabolites that inhibit dopamine beta-hydroxylase leading to increase the formation of dopamine. Altered gut microbial composition observed in Schizophrenia is specific relative to the gut microbiome. Fecal microbiota transplantation (FMT) experiments in mice which was transplanted with schizophrenia microbiota displayed locomotor hyperactivity, decreased anxiety and depressive-like behaviors, and increased startle responses.\[11\]

**GBA and irritable bowel syndrome**
Alterations in gut microbiota result in HPA axis abnormalities, which lead to increased corticotrophin-releasing hormone (CRH) synthesis. CRH affects motility and sensitivity in the gut causing diarrhea. It has been also seen that dysfunction with impaired parasympathetic function causes alternating diarrhea/constipation (influenced by social stressors). Altered GBA associated with low-grade inflammation in the gut leads to alterations in intestinal motility and sensations. Neuroimaging in the form of functional MRI studies reveals heightened metabolic activity in the anterior cingulated, prefrontal cortex, and the insula in patients with irritable bowel syndrome.

**CLINICAL IMPLICATION**
Main strategies for manipulating gut microbiota can be done by immune response by vaccination or by combination of antibiotics, probiotics, or fecal transplant.

**Fecal microbiota transplantation**
It helps in the treatment of severe clostridium difficile colitis when pseudomembranous colitis is not responsive to antibiotics such as metronidazole and vancomycin.

**Bacteriophage therapy**
It helps in targeting bacterial genes to suitably modify the microbiome.

**Psychobiotic effect**
Bacteria-based interventions can indeed have a positive effect on mental health.

**WHY STILL A CONCEPT?**
There had been substantial gap between the animal research findings and the clinical data on humans. Few studies have found significant decreases in depressive symptoms for subjects with depressive disorder.
use of probiotics leads to reductions in symptoms of depression and anxiety, improves mood, and reduces stress response. However, more trials are necessary to use probiotics in mental health.

**CONCLUSION**

There is bidirectional communication network between gut and brain which includes gut microbiota and their metabolic products, ENS, sympathetic and parasympathetic branches, neural-immune system, neuroendocrine system, and CNS. There are different routes of communicating between gut microbiota and brain. In this communicating network, the brain affects gut movement, sensory and secretion function, and viscera signal from the gut also affects brain function. The role of microbiota is rapidly emerging in gut–brain communication, and alterations in the composition of gut microbiota have been observed in several diseases.

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There are no conflicts of interest.

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