WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 8, 462-473. Review Article ISSN 2277–7105

MICROBIAL MEDIATORS OF THE GUT-BRAIN AXIS: IMPLICATIONS FOR NEUROLOGICAL AND PSYCHIATRIC DISORDER

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Article Received on
22 February 2025,

Revised on 14 March 2025,
Accepted on 04 April 2025

DOI: 10.20959/wjpr20258-36250

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ABSTRACT

The human gut microbiome comprise a huge number of microorganisms with coevolutionary associations with humans. It has been repeatedly revealed that bidirectional communication exists between the brain and the gut and involves neural, hormonal, and immunological pathways. Evidences from neuroscience researches over the past few years suggest that microbiota is essential for the development and maturation of brain systems that are associated to stress responses. This review summarizes recent data on the role of microbiota- gut-brain axis in the pathophysiology of neuropsychiatric and neurological disorders including depression, anxiety, schizophrenia, autism spectrum disorders, Parkinson‟s disease, migraine, and epilepsy.

KEYWORDS: Microbiota Gut-Brain Axis, Gut Microbiota, Probiotics, Enteric Microbiota.

INTRODUCTION

The origin of “microbiota” can be dated back to early 1900s. It was found that a vast number of microorganisms, including bacteria, yeasts, and viruses, coexist in various sites of the human body (Gut, Skin, Lung, Oral cavity). In addition, the human microbiota, also known as “the hidden organ,” contribute over 150 times more genetic information than that of the entire human genome. Although “microbiota” and “microbiome” are often interchange-able, there are certain differences between the two terms. Microbiota describes the living microorganisms found in a defined environment, such as oral and gut microbiota. The human gut possesses millions of microbes that define a complex microbial community. The gut microbiota has been characterized as a vital organ forming its multidirectional connecting

axis with other organs. This gut microbiota axis is responsible for host-microbe interactions and works by communicating with the neural, endocrinal, humoral, immunological, and metabolic pathways. The human gut microorganisms (Mostly non-pathogenic) have symbiotic host relationships and are usually associated with the host‟s immunity to defend against pathogenic invasion. The dysbiosis of the gut microbiota is therefore linked to various human diseases, such as anxiety, depression, hypertension, cardiovascular diseases, obesity, diabetes, inflammatory bowel disease, and cancer. Irritable bowel syndrome (IBS) is the most prevalent disorder of gut-brain interaction (DGBI), char-acterized by abdominal pain associated with altered bowel habits. The majority of patients also report associated anxiety and depression. microbiota has recently gained much attention. The term "microbiota" refers to consortia of microorganisms living in a defined environment, while the term "commensals" refers to micro-organisms that colonize host without causing a disease.

Gut microbiota

The human gastrointestinal (GI) tract represents one of the largest interfaces (250–400 m2) between the host, environmental factors and antigens in the human body. In an average life time, around 60 tonnes of food pass through the human GI tract, along with an abundance of microorganisms from the environment which impose a huge threat on gut integrity. The collection of bacteria, archaea and eukarya colonising the GI tract is termed the „gut microbiota‟ and has co-evolved with the host over thousands of years to form an intricate and mutually beneficial relationship. The term microbiota refers to microbial communities that include bacteria, archaea, eukaryotes, and viruses that are present in a host. Among them, bacteria are predominant, particularly certain types of bacteria. A meta genomics analysis of the gut microbiome in 124 subjects (a cohort composed of healthy subjects, overweight subjects, and inflammatory bowel disease [IBD] patients) showed that 99% of the genes were bacterial, and 1,000-1,150 species were found in the entire cohort. Each individual harbored at least 160 bacterial species and more than three million microbial genes.

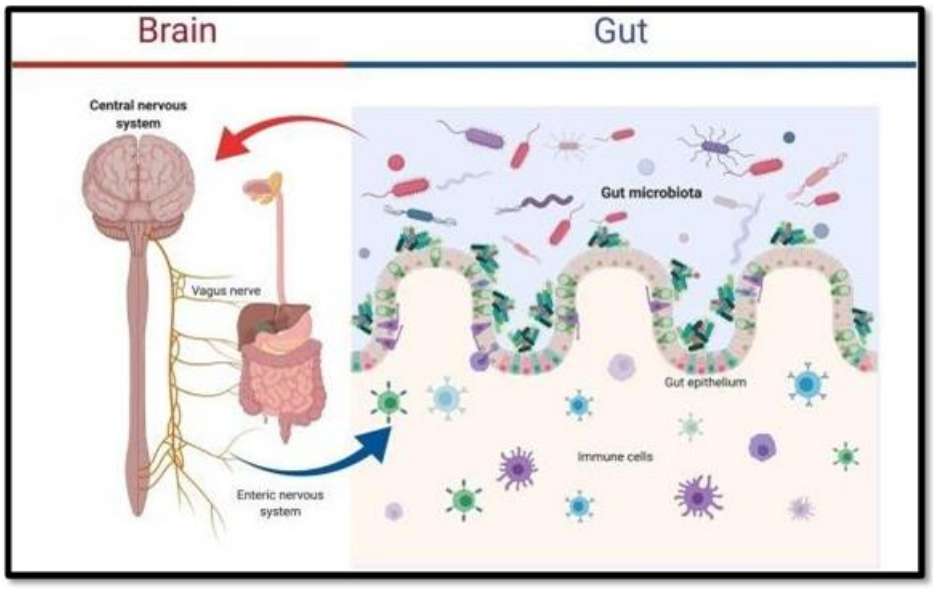

Fig. 1: Structure of gut microbiota.

Development of gut microbiota

The gut microbiome varies according to age and is generally formed in three stages. Because the inside of the uterus is aseptic, an infant is sterile until birth. When passing through the birth canal, an infant encounters some bacteria, which then colonize the gastrointestinal tract, mouth, skin, and conjunctiva. The gut microbiota acquired during vaginal delivery include Bifidobacterium, Lactobacillus, and Prevotella as predominant genera. Staphylococcus and Corynebacterium are the main genera acquired by newborns born via cesarean section. The gut microbiome of a newborn is representative of the bacterial composition of the external environment and the maternal skin, and the birth method greatly affects the initial microbial settlement. Breastfed infants at this early stage have a lower diver-sity of gut microflora than infants fed formula, but the composition tends to be more stable. After initiating solid foods, the diversity of the gut microbiota increases. The proportion of anaerobic bacteria classified as Firmicutes begins to increase, and the microbiome becomes similar to that of an adult gut by three years of age.

The microbiota-gut-brain axis in neuropsychiatric diseases

Depression and anxiety Major depression is one of the most common psychiatric diseases with multifactorial etiology. It is associated with structural and funcional brain abnormalities within the hippocampus and the prefrontal cortex. Stress is considered as a precipitant of depression, whereas the HPA axis dysfunction is observed in depressed patients and in animal models of this disease. Animal models of depression are often based on exposure to stress. Furthermore, almost two-thirds of individuals with major depressive disorder have

anxiety which can manifest both as comorbidity and as a predominant feature. Animal models often manifest anxiety-like behavior in parallel to depression-like behavior. The relationship between stress-induced diseases and the intestinal microbiota is receiving much attention. Data suggest that the gut microbiota plays an underlying role in several stress-associated neuropsychological conditions, including anxiety and depressive disorders. The data on the role of the GI microbiome in modulating stress-induced changes in behavior and brain functioning are mainly provided by preclinical studies. In this part of our article, we review the preclinical, as well as clinical, reports on the role of the intestine microbiota composition in the pathology and therapy of depressive disorders and anxiety.

Neurodegenerative diseases

Neurodegenerative diseases are a collection of neurological diseases that are characterized by progressive loss of neurons, including AD, Parkinson‟s disease (PD), amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS). Each of the neurodegenerative diseases has been reported to have unique pathologies and clinical features. Nevertheless, neuroinflammation and higher intestinal permeability are common characteristics of them.Some of the peripheral inflammation factors such as TNF-α, iNOS, and IL-6 have been validated in the pathogenesis of the neurodegeneration in CNS. In this chapter, we will discuss how functional gastrointestinal disorders are critically linked to these neuropathies.

Parkinson's disease

PD is a typical neurodegenerative disorder affecting more than 1% of the population over 65 years of age. PD is thought to be caused by the interaction between environmental and genetic risk factors. This neuropathology is characterized by motor deficits and non-motor symptoms (NMS), which ultimately have an impact on quality of life. Recently, the gut microflora has drawn increasing attention with respect to how it may be implicated in PD. A variety of enteral dysfunctions are associated with PD, such as SIBO, malnutrition, H. pylori infection, and constipation. In terms of the role of GI tracts pathology in PD, a higher frequency of α-synuclein detection is found in the patients than in controls from many researches. Animal studies validated that resection of vagus nerve can stop transmission of α-synuclein from gastro intestine to the CNS. Bowel inflammation can also trigger neuroinflammation to promote dopaminergic neuronal loss in the rodent.

Migraine

Migraine is one of the most disabling medical conditions. The Global Burden of Diseases, Injuries, and Risk Factors Study identifies migraine as a leading cause of disability worldwide, particularly in individuals younger than 50 years. The 1-year prevalence of migraine in the general population is 12%. The annual and lifetime prevalence are 18% and 33% in women, and 6% and 13% in men, respectively. This chronic neurological disorder is characterized by attacks of headache and reversible neurological and systemic symptoms. The most characteristic symptoms include photophobia, phonophobia, cutaneous allodynia, and GI symptoms such as nausea and emesis. Other GI symptoms include constipation or diarrhea. Furthermore, there is an association between migraine and GI disorders such as inflammatory bowel disease or IBS. The prevalence of Helicobater pylori infection is also significantly greater in migraineurs than in controls (44.97% vs 33.26%, respectively). Moreover, abdominal migraine is among pediatric functional abdominal pain disorder and is currently referred to as a disorder of the gut-brain axis.

Probiotic supplementation could enhance the gastric emptying rate and attenuate gastric stasis in migraineurs. However, a meta-analysis of randomized placebo-controlled trials on the use of probiotics in the prophylaxis of migraine according to the PRISMA guidelines was not possible due to methodological differences. Qualitative comparison of the studies demonstrated a dichotomy of results one trial reported no significant change in migraine frequency and intensity, while the second trial reported highly significant improvements. However, concerns have been raised about the statistical analysis (paired t-test within groups) in the study which did not show change in migraine frequency after administration of probiotics. Recently, another study, which was not included in the systematic review, showed reduction in the mean frequency of migraine after the use of symbiotic. Noteworthy is the fact that the interventions used differed in terms of the composition as well as concentration of bacteria. Currently, the evidence supports a call to action for microbiome research in migraine, in order to build the evidence base regarding nutrition‟s potential impact on migraine attack prevention and treatment.

Roles of microglia in neurodegenerative diseases

Microglia are the primary innate immune cells of the CNS, accounting for nearly 10% of CNS cells. Although microglia were erroneously considered inert bystanders of CNS disorders, they possessed diverse context-dependent functions central to CNS development, homeostasis, and diseases. Under homeostatic conditions, microglia contribute to the

regulation of numerous physiological functions, including neurogenesis, angiogenesis, maintaining BBB integrity synaptic pruning and remodeling, synaptic transmission myelin health, as well as phagocytosis and removal of apoptotic neurons and cellular debris.

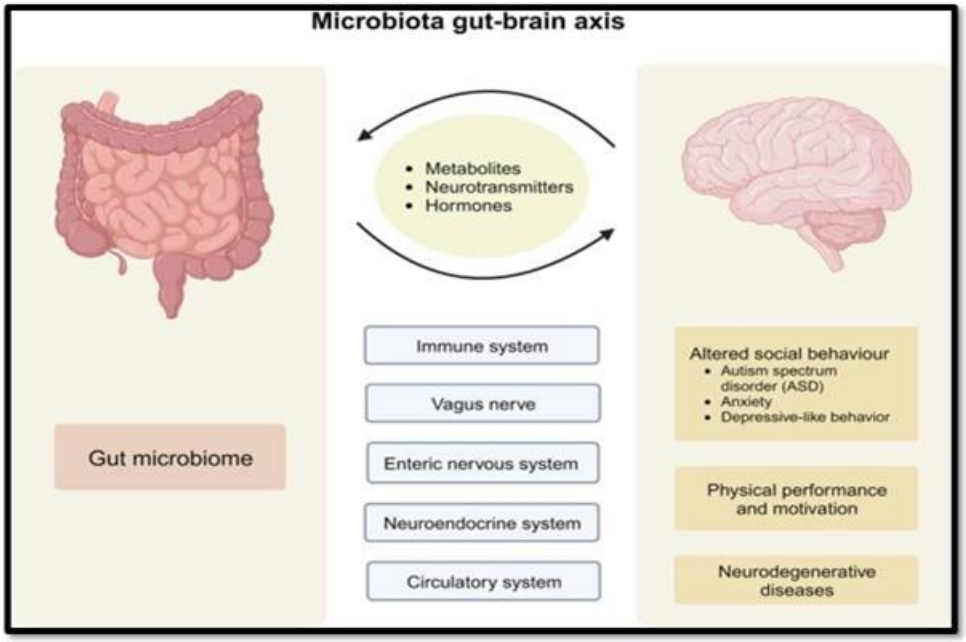

Fig. no. 2: Microbiota gut brain axis.

The microbiota–gut–brain axis. The bidirectional communication between the gut microbiome and the brain is mediated by the immune system, vagus nerve, enteric nervous system, neuroendocrine system, and circulatory system. Alterations in gut microbiota have been linked to the development of autism spectrum disorders, anxiety, depressive-like behavior, impaired physical performance, and motivation, as well as neurodegenerative diseases.

Pathways of the Gut-Brain Axis

As early as 1998, oral administration of a single, unique bacterium (Campylobacter jejuni) to rats in subclinical doses was found to lead to anxiety-like behavior, without an accompanying immune response. Later research confirmed that introduction C jejuni caused anxiety-like behavior in mice, with concomitant activation of neuronal regions in the brain that were dependent on information received from the gut via the vagus nerve. The seminal first studies establishing mechanisms of the gut-brain axis made use of animals raised in a sterile environment. Sudo et al14 sought to answer the question of whether postnatal microbial colonization could affect the development of brain plasticity and subsequent physiological response. To test the idea that gut microbes might affect the development of neural systems

that govern the endocrine response to stress, they studied the HPA axis reaction to stress by comparing germ-free (GF), specific pathogen free (SPF) and gnotobiotic mice. They found that colonizing microbes altered the HPA response to restraint stress, indicating that the interaction of gut bacteria with the brain is also bidirectional, just like the brain-gut axis. This was the first report to show commensal microbes affecting the neural network responsible for controlling stress responsiveness.

Neurologic pathway

The neurologic pathway includes the vagus nerve, the enteric nervous system, and the activity of neurotransmitters within the GI tract. Neurologic modulation of afferent sensory nerves directly produces molecules that can act as local neurotransmitters, such as GABA, serotonin, melatonin, histamine, and acetylcholine; this pathway also generates biologically active forms of catecholamines in the lumen of the gut.2 The autonomic nervous system also influences immune system activation in the gut, for example by directly modulating macrophage and mast cell responses to luminal bacteria. In addition, the gut microbiome appears to be essential for normal gut intrinsic primary afferent neuron excitability.

Immune pathway

Inflammation metabolism within the GI tract is influenced by the gut microbiome, principally via the immune systems release of cytokines (such as interleukin [IL]-10 and IL-4) and other cellular communication mediators, such as interferon-gamma, during times of dysbiosis. In irritable bowel syndrome (IBS), as an example, abnormal microbiota populations activate mucosal innate immune responses, which increases gut epithelial permeability, activates gut pain sensory pathways, and dysregulates the enteric nervous system both brain-gut and gut-brain dysfunctions occur, the former being dominant. Disruptions in the gut-brain axis affect intestinal motility and secretion, contribute to visceral hypersensitivity and lead to cellular alterations of the entero-endocrine and immune systems.

Intervention to improve microbiota gut–brain axis

In this section, we outline INTERVENTION TO IMPROVE MICROBIOTA–GUT–BRAIN AXIS In this section, we outline three potential points of interventions to regulate the microbiota–gut–brain axis, namely the intestinal barrier, BBB, and meninges. We provide evidence that dysfunctional barrier integrity induces glial activation and neurodegeneration. Thus, restoring the integrity of these biological barriers holds promise in counteracting dysfunctional glial states in neurodegenerative diseases. Among the biological barriers,

targeting the intestinal barrier represents the most promising and straightforward approach, given the direct interactions between gut microbiota and the intestinal barrier. In addition, Microbiota–gut–brain axis and its Loh et al 18. Signal Transduction and Targeted Therapy (2024) potential points of interventions to regulate the microbiota–gut–brain axis, namely the intestinal barrier, BBB, and meninges. We provide evidence that dysfunctional barrier integrity induces glial activation and neurodegeneration. Thus, restoring the integrity of these biological barriers holds promise in counteracting dysfunctional glial states in neurodegenerative diseases.

Factors affecting the structure of the gut microbiome

Long-term dietary habits are associated with gut microbiome compositions. People with high protein and animal fat diets have enterotypes characterized by high levels of Bacteroides, while those who eat a high fiber diet have entero-types characterized by high levels of Prevotella. Prebiotics refer to indigestible food ingredients that selectively stimulate the growth and activities of beneficial microorganisms, such as Lactobacillus and Bifidobacterium. Infection, antibiotics, and other factors can temporarily alter the stability of the gut microbiota composition, which might have detrimental effects on the host. Even the short-term use of antibiotics can lead to long-term dysbiosis, inducing accelerated maturation and exacerbation of diseases. The subject of stress-induced changes in the gut microbiome represents a challenging topic and will be discussed in more detail in this article.

Pathophysiology of the microbiota-gut-brain axis in neuropsychiatric illnesses

Stress and Anxiety

Anxiety is an emotional state that develops via neural, endocrine, and immunologic mechanisms. Exposure to stress (including biological, environmental, or psychological stimuli) can provoke anxiety responses involving activation of the HPA axis or the immune response. The coexistence of anxiety and acute or mild intestinal dysfunction has been documented extensively, and the role of gut-brain signals, such as neurotransmitters and immunologic factors, has been emphasized. Germ-free mice show increased motor activity and lower anxiety compared to SPF mice with normal microbiota. A reduction of anxiety behaviors in the GF condition is associated with elevated 5-HT and tryptophan metabolism and with long-lasting modulation of synaptic transmission by reducing PSD-95 and synaptophysin expression. These findings imply that gut microbiota regulate the degree of the HPA axis response. Dysbiosis caused by pathogenic bacteria in the intestine can induce and

exacerbate anxiety via immunologic and metabolic pathways of the MGB axis.

Depression

Depression is a mood disorder associated with imbalance of the HPA axis, dysregulation of the immune system, and deficiency of tryptophan metabolism. Although it is not known whether an imbalance of intestinal microorganisms is the cause or the effect of depression, several observtional studies show a bidirectional interaction between depression and the gut microbiome. Depression is associated with dysregulation of the HPA axis. Profound changes in gut commensals were observed in mice that experienced maternal separation. De Palma et al. reported behavioral despair with changes in the HPA axis in maternal-separated rats. A direct association between microbes and the HPA axis can be seen by the increased corticosterone and adrenocorticotropin responses to restraint stress in germ-free (GF) mice compared to specific pathogen-free (SPF) mice.

Metabolites produced by gut Microbiota and Their functions.

Metabolites	Functions
Bile acid metabolites; including deoxycholic acid(DCA) and lithocholic acid (LCA)	Regulate bile acid, cholesterol, lipid, glucose, and energy metabolism, show antimicrobial effects, and activate host nuclear receptors and cell signaling pathways.
Short-chain fatty acids (SCFAs) metabolites such as propionate and butyrate	Regulate food intake and insulin secretion, also aid in maintaining body weight.
Branched-chain fatty acids (BCFA) including isobutyrate, isovalerate	Histone deacetylase (HDAC) inhibition, increased histone acetylation.
Indole derivatives including indoxyl sulfate and indole-3-propionic acid (IPA)	IPA exhibits neuroprotective effects, acts as a powerful antioxidant, and regulates intestinal barrier function. Indoxyl sulfate is a uremic toxin that accumulates in the blood of individuals with impaired excretion systems.
Vitamins including thiamine (B1), riboflavin (B2), niacin (B3), pyridoxine (B6), pantothenic acid (B5), biotin (B7), folate (B11-B9), cobalamin (B12), and menaquinone (K2)	Help in red blood cell formation, DNA replication, and repair, work as an enzymatic co-factor, and enhance immune functioning.
Ethanol	Protein fermentation metabolites may be involved in NAFLD progression.
Hydrogen sulfide (H2s)	Reduction/neutralization of reactive oxygen spacies

Treatments targeting the gut microbiota for neuropsychiatric illnesses

Probiotics

Probiotics are defined as live microorganisms that provide health benefits to humans or animals when consumed. Lactobacillus and Bifidobacterium species account for most probiotics. Animal studies on probiotic involvement in various neurological diseases have been performed, and many promising results have been reported. There are many studies on probiotics, but only studies reporting changes in neuropsychiatric symptoms in healthy subjects or in subjects with neuropsychiatric illness will be described in this review. Most of these are studies on cognition, autism spectrum disorder, or anxiety and depressive-like behavior. Studies on probiotics with positive results have shown that low-grade inflammation is reduced, neurotrophic factors such as BDNF are modulated, gut permeability is restored, and the composition of the gut microbiome changes.

Clinical evidences of gut-microbiota targeting treatments.

Clinical Concern	Target Population	Treatment	Evaluation Tool	Behavioral and Psychological Outcomes	Biological Outcome
Anxiety and cognition	Healthy volunteers	B-GOS	Emotional processing tasksAttentional dot-probe task Facial expression recognition task Emotional categorisation and memory	Increased vigilance attention	Decreased waking cortisol level
Anxiety and Depression	55 Healthy volunteers	L. helveticus, B. longum	HSCL-90, HADS, PSS	Improvement of anxiety and depression	Decreased urinary free cortisol
IBS severity	74 IBS patients	L. bulgaricus, S. thermophiles, L. paracasei, L. acidophilus	HADS	No change in HADS	IBS severity was similarly improved between treatment and control groups
Stress and anxiety	140 Healthy medical students	L.casei Shirota	STAI	No change in self-reported anxiety	Decreased salivary cortisol level
Schizophreni a	65 Schizophre nia patients	L. rhamnosus, B. animalis	PANSS	No difference of PANSS	Bowel movement im-provement

Anxiety and Depression	70 healthy petrochemi - cal workers	L. acidophilus, L. casei, L. rhamnosus, L. bulgaricus, B. lactis, B. breve, B. longum, S. thermophilus	GHQ, DASS	Improvement of anxiety and depression	No changes in HPA axis activity

CONCLUSION

Many recent studies over the last decade have played an important role in recognizing the importance of gut microbiota in brain function. The results of major studies show that the bidirectional interaction between microorganisms and the brain affects various CNS activities (Such as stress response, behavior, and mood) through immune and neuroendocrine system pathways. It is now clear that the gut microbiota directly or indirectly affect neuropsychiatric illness. Whether microbial dysbiosis is the cause or a complication of illness must be further investigated.

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