Interactions of Microbiome for Gut-Brain Axis Health

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Abstract

The various types of interactions between the gut microbes and the brain have engrossed the interest of researchers in recent times in the context of precision medicines for a variety of diseases. People infected by human immunodeficiency virus (HIV) face neurocognitive fall in comparison to the general population, thus disrupting the persistent composition of the gut microbiome, i.e., dysbiosis. The signaling between the microbiota-gut-brain axis (MGBA) can occur through various types of pathways that involve number of host neurochemical signaling, immune system, direct enteric nervous system routes, vagus nerve, and various types of secondary metabolites. Various neurological and psychiatric disorders often occur due to the alteration in the gut microbial profiles. The cutting-edge research highlights the concept of direct relationship between gut microbiota and psychological status of a person and the role of probiotics on the regulation of human neurocognitive health.

Keywords

Brain · Gut · Gut-brain axis · Mental development · Microbiota · Probiotics

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5.1 Introduction

The microbiota existing within the gut comprise bacteria, protozoa, archaea, fungi, and virus that live within the human gastrointestinal tract (GIT). It has been observed that the number of bacterial cells found within the human body exceeds the number of human body cells (Sender et al. 2016), and they play an important role in the maintenance of physiological activities within the human being. It has been observed that mitochondria, which are important for the generation of adenosine triphosphate, originate from bacteria and related to Proteobacteria (Roger et al. 2017). The major group of microbial species in the gut belongs to *Bacteroides* and Firmicutes, but there exist a large number of individual microbial communities, and the terms "dysbiosis" and "healthy gut microbiome" remain controversial (Moloney et al. 2014).

Intercommunication between GIT, peripheral and central nervous system (PNS and CNS) and the microorganisms results in the development of MGBA and thereby causes the transmittance and interpretation of information from periphery to the brain and back. This complex system of communication helps in the maintenance of coordination of gastrointestinal functions, which supports the physiological and behavioral processes (Mörkl et al. 2020). The exact mechanism of gut-brain communication helps in the coordination and maintenance of gastrointestinal functions and various physiological processes. It also has its effect on behaviors, mood, and other cognitive functions. The exact mechanism of communication is still under various studies that involve endocrine pathways comprising cortisol and hypothalamic-pituitary-adrenal (HPA) axis, nervous pathways comprising vagus nerve and enteric nervous system, and immune pathways. Psychiatric disorders often result in the alteration in these pathways.

Various types of microbial flora are inherited at the time of birth, and it shows change depending on the dietary habits and various environmental signals (Gomez de Aguero 2016. Koh et al. 2016, Wahlstrom et al. 2016). Changes in the gut microbiome has severe effect on immune signaling, thus resulting in illness associated with the intestine and distal organs comprising inflammatory bowel diseases (IBD), various types of cancer, and autoimmune diseases (Blander et al. 2017; Roy and Trinchieri 2017). Various types of intrinsic and extrinsic determinants play an important role in the maturation and development of the CNS. It has been further observed that germ-free animals or animals' exposure to broad-spectrum antibiotics often has an effect on their CNS physiology and neurochemical signal transduction (Smith 2015).

In recent times, the target for epigenetic modification is the gut microbiota (Gomez de Aguero 2016) that can be used for treating psychiatric disorders to improve symptoms. Administration of probiotics in adequate proportion provides health benefits to the host (Butel 2014). Improvement in the microbiota-gut-brain axis (MGBA) can be achieved by the use of prebiotics comprising diet rich in nondigestible fibers and modified dietary components, antibiotics, synbiotics (a combination of pre- and probiotics), probiotics comprising fermentation products, and transplantation of fecal microbiota (Zmora et al. 2019). These are considered as

the potent psychobiotics as they can be used for the purpose of mental health by modifying the microbiota (Dinan et al. 2013; Sarkar et al. 2016). This review highlights the role of brain-gut-microbiota axis on mental makeup and outlines the new definition of psychobiotics, including both pre- and probiotics, which play a pivotal role in influencing bacteria-brain relationships.

5.2 Profile of Gut Microbiota

The bidirectional communication existing between the gut and the brain is an obvious process responsible for controlling safety signals, hunger, and the factors responsible for the intake of food (Konturek et al. 2004). This type of communication is also responsible for maintenance of social behavior, stress response, and fear expressions. Alteration in this behavior is due to illness associated with GI and results in the discomfort associated with GI. It has been further observed that anxiety, acute and chronic stress, and depression also bring about change within the gut microbiota profile (Dinan et al. 2018). The colonization of microbiota occurs within the gut which gets initially seeded from the maternal vagina (Dominguez-Bello et al. 2010). The microbiota of infants delivered via cesarean section (C-section) differs from those born via vaginal delivery. The microbiota of infants delivered via cesarean section comprise of microbes seeded from the skin and delivery suite (Ng 2000) and possess lesser amount of colonization by *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*. The microbiota thriving within the body of infants born via C-section takes nearly 2 years to resemble the microbiota of infants born via vaginal delivery (Hill et al. 2014), but the differential seeding mechanism often results in the relative risk in childhood causing asthma (Metsala et al. 2015) and obesity (Mueller et al. 2015). The microbiota composition in the early life is dependent on various factors comprising the parent use of antibiotics, geography, breastfeeding, and growth in early years of life (Vatanen et al. 2019). Diet plays a vital role in the maintenance of the composition of the gut microbiome, and change in diet alters the microbiota (David et al. 2014) (Fig. 5.1).

5.3 Signaling Mechanism Associated behind MGBA

Various mechanisms are associated with the signaling (Table 5.1) of MGBA (Fig. 5.2). The microbiota associated with the gut is responsible for the production of bioactive peptides comprising branched-chain amino acids, short-chain fatty acids (SCFAs), gut hormones, and neurotransmitters and transformation of the secondary bile acids. The short-chain fatty acids possess the ability to enter to the bloodstream and act as a possible route for the signal to reach up to the brain (Sarkar et al. 2016). Microbes are responsible to bring about metabolism of tryptophan, thus modulating the serotonin signaling (Kennedy et al. 2017). Gut microbes are responsible for the synthesis of acetylcholine, noradrenaline, dopamine, and GABA (Clarke et al. 2014). The walls of the gut comprise enteric nervous system that are mainly

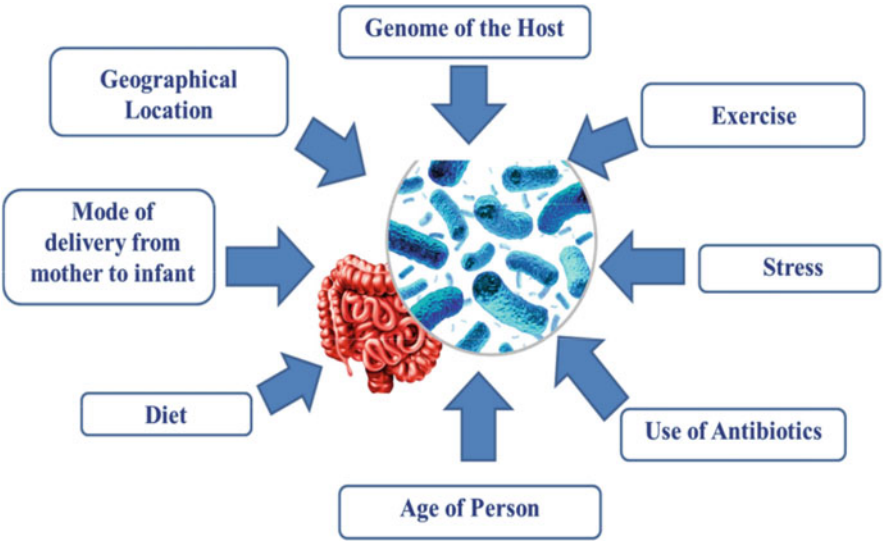

Fig. 5.1 Factors responsible for the maintenance of the gut microbiota

Table 5.1 Different signaling pathways influencing gut microbiota

Type of communication	Mechanism	Reference
Inflammatory signal pathway	Diverse groups of microbial and endogenous signals are responsible for the activation of inflammasome. NLRP6 is an inflammasome signaling that helps in the modulation of the microbiota. Deficiency of NLRP6 results in the distortion of colonization, thereby leading to dysbiosis	Levy (2015)
Type I interferon signaling pathway	Interferon I (IFN-I) plays an important role in the modulation of microbiota. It has been observed that *Lactobacillus acidophilus* possesses the ability to induce antiviral response associated to TLR-2-dependent INF-β. it has been also observed that *Clostridium orbiscindens* helps in the protection of mice from influenza through IFN-I signaling	Weiss (2010) and Steed (2017)
NF-kB signaling pathway	Change in the composition of microbiota results in various inflammatory diseases by the regulation of innate immunity especially by NF-kB signaling. The dysbiosis of the intestine resulting in the killing of *Campylobacter jejuni* causes the activation of NF-kB under the influence of various cytokines that further results in the activation of various immune cells	Masanta (2013)

responsible for the motility of neurotransmitter and short-chain fatty acids (Rea et al. 2016). The gut also comprises immune cells that provide second line of defense against the pathogens after the mucous layer of the gut epithelium, which acts as a

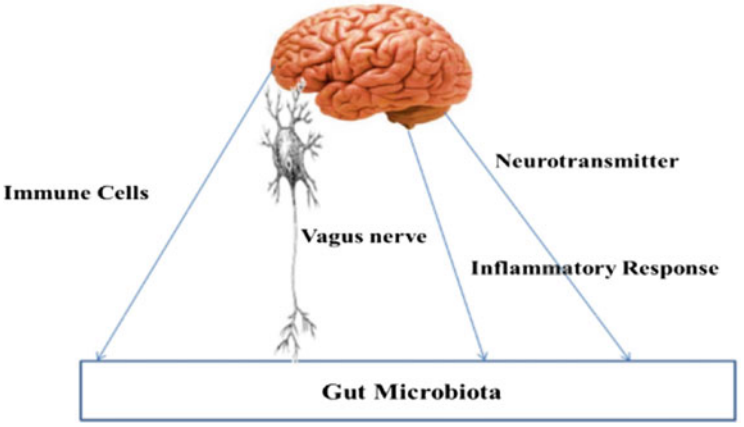

Fig. 5.2 Mechanism of communication between the brain and gut microbiota

physical barrier. Gut microbiota is also responsible for the production of anti- and pro-inflammatory cytokines that act as a signal to the brain via the circulatory system. The permeability of the gut is negatively affected at the time of stress (Vanuytsel et al. 2014). The vagus nerve is regulated by the MGBA signaling (Fig. 5.2), which helps in the maintenance of the communication taking place between the brain and the gut (Fulling et al. 2019). For example, Parkinson's disease can be prevented by the mechanism of vagotomy, which is a surgical method to treat peptic ulcer disease, thereby reducing the possibility of the implication of *Helicobacter pylori* in this disease (Svensson et al. 2015).

5.4 Role of Gut Microbiota in the Development of Brain Behavior

The understanding of the importance of gut microbiota (GM) in the development of the brain and mental state brought about a total paradigm shift in the field of psychology. GM is not only responsible for developing the function of gut-brain but also has its impact on the brain and behavior (Kundu et al. 2017). The disturbance of the microbiota results in the development of mental and brain-associated disorder (Dinan and Cryan 2017). The microbiota present within the infants enhances phylogenetically after birth and resembles the adult form within a 3-year period (Bokulich et al. 2016). The diversification of phylogeny of the microbiota keeps on increasing, but adolescence has a great impact on the composition of the microbiota (Kundu et al. 2017). Gut microbiota plays a vital role in the maintenance of the behavior and mind of the host, but its relevance is often ignored (Vuong et al. 2017). It plays an important role in the perseverance of visceral and peripheral pain response. It has been further observed that supplementation of probiotics after the treatment of antibiotics often results in the suppression of pain sensitivity (Vuong

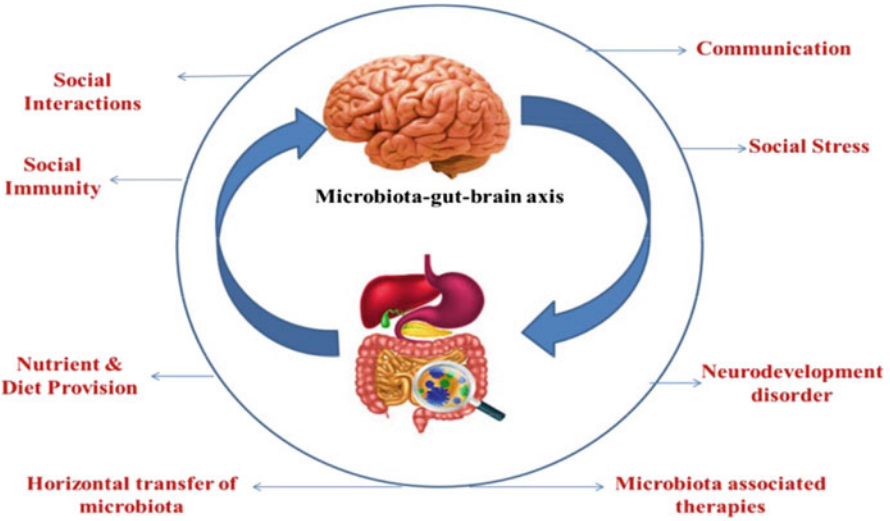

Fig. 5.3 Gut-brain microbiota interaction affecting human activities and management of stress

et al. 2017). Abnormal composition of gut microbiota often results in myalgic encephalomyelitis/chronic fatigue syndrome, and its symptoms can be altered after the supply of probiotics (Rao et al. 2009). Abnormal microbiota is also associated with various pain-associated disorders like migraine, abdominal pain, and chronic back pain (Gawronska et al. 2007). The learning capacity and memory are largely associated to the microbiota being present within the gut (Manderino et al. 2017). It has been often observed that administration of antibiotics often results in the damage of spatial and working memory, which improves with the administration of probiotics (Vuong et al. 2017). It has been often observed that infliction of pathogenic infections results in the development of sickness behaviors with various symptoms comprising social avoidance, fatigue, decreased appetite, and enhancement in anxiety (Gur et al. 2015).

The character and temperament of a person are closely associated with the gut microbiota that possesses the ability to get transplanted from one person to another by the fecal microbiota transplantation (Kim et al. 2017). Management of stress is also associated with the gut microbiota (Fig. 5.3), which plays a vital role in the stress response (Luczynski et al. 2016). It has been observed that psychological stresses help in the activation of neuroendocrine, nervous, and immune systems but also bring about alteration in the mood and gut microbiota (Bharwani et al. 2016). Healthy microbiota helps the host to cope up with stress, whereas alteration in the microbiota enhances the susceptibility of the host to various types of disorders (Vuong et al. 2017).

5.5 Control of Microbiota on the Brain Through Nervous Pathway

Microbiota affects the brain and behavior at a very fast rate via the nervous pathway (Table 5.2). This entire mechanism comprises neural conduction, neurotransmitter, neurogenesis, neurodegeneration, and apoptosis (Thion et al. 2017). Various neuro-endocrine pathways are influenced by the gut microenvironment, which is actually maintained by the microbiota.

5.6 Controlling of the Immune System by Gut-Microbiome

The microbiota plays an important role in the maintenance of the immune system. The immunity associated gut mucosa is one of the important parts of the immune system, and immune cells present within the gut-associated lymphoid tissue account for 70–80% of the total immunologically active cells (Tlaskalova-Hogenova et al. 2005). Immune cells bring about regulatory effect upon our body in symbiotic relationship with that of the microbiota. It has been observed that alteration or absence of gut microbiota results in immune deficiency (Gensollen et al. 2016). The gut microbiota helps in the development of adaptive and innate immunity, thus influencing inflammation and neuroimmunity (Freestone et al. 2008).

Table 5.2 Nervous pathways and microbial interaction

Types of nerve pathways	Involvement of microbiota	Reference
Neural conduction	The metabolites produced by the microbiota and its types play a vital role in regulating the activities of the cranial nerves. The microbiota possesses the ability to affect the brain via vagus nerve. The primary afferents possess the ability to first release the impulse, which in turn activates the vagus nerve, thereby sending it to the brain. The microbiota possesses the ability to recognize the signal released by the host and enact promptly	Liang et al. (2018)
Neurotransmitters	Body alone is unable to bring about regulation of neurotransmitter, but microbiota have an important role in the maintenance of neurotransmitters within the body. Gut microbiota possesses the ability to produce a neurotransmitter by altering the metabolism pathways of a neurotransmitter	Liang et al. (2018)
Neurogenesis, neurodegeneration, and apoptosis	The gut microbiota plays an essential role in the maintenance of various physiological activities. The pH concentration of the gut	Liang et al. (2018)

5.6.1 Innate Immunity

GM plays a vital role in the functioning and maturation of the innate immunity. The microbiota regulates the development and functioning of the immune barrier and also helps in the regulation of innate immune cells and pattern recognition receptors (Tlaskalova-Hogenova et al. 2005). The functioning of the blood-brain barrier (BBB) and gut barrier is dependent upon the gut microbiota. Deficiency of the barrier caused by microbiota enhances susceptibility toward various types of diseases (Gensollen et al. 2016). Downregulation of the expression of tight junction, permeability of the BBB, and induction of leaky brain are observed in the absence of microbiota (Kelly et al. 2015). Abnormality in gut microbiota often results in the induction of stress-related disorders and various neurodegenerative diseases (Hoffman et al. 2017).

5.6.2 Adaptive Immunity

The development of adaptive immunity takes place at the time of exposure and combating with microbiota. The process of differentiation and functioning of lymphocytes is dependent on the gut microbiota that further influences the synthesis and release of antibodies (Artis 2008). The immune system possesses the ability to differentiate pathogenic and beneficial group of bacterial cells and possesses the ability to tolerate self-components and harmless materials when exposed to microbiota during early life (Knoop et al. 2017). The gut microbiota helps in regulating the CD4+ T cells and differentiates them to T lymphocytes, which further produce pro-inflammatory responses (Honda and Littman 2016).

5.7 Brain Disorder and Altered Microbiota

Alterations in the gut microbiota result in the development of diseases. Differences in the microbial profiles result in the development of Alzheimer's disease (AD) and various psychological disorders (Table 5.3).

5.8 Therapeutic Target of Gut-Brain Axis

Probiotics are live microorganisms administered in adequate amounts within the host body that have a beneficial effect on human health. The use of probiotics showed its efficacy (Table 5.4) in reducing anxiety-like behavior, depression, and stress within an animal model. Bacterial species like *Bifidobacterium* and *Lactobacillus* are used as probiotics to a large extent. Probiotics do not reside within the gut, but the probiotic formulation requires regular consumption to maintain its positive effect. Probiotics act as components of food that are provided as supplement (O'Toole et al. 2017).

Table 5.3 Microbiota and CNS-associated disorders

Name of the disease	Description	Reference
Multiple sclerosis	It is characterized by immune-associated demyelination of neural axon. Pathogenesis of this disease originates within the immune system and possesses significant contribution of both environmental and genetic factors. Gut microbiota is associated with immune signaling and physiological processes. Thus, it has a control on the pathogenesis at the time of multiple sclerosis	Berer et al. (2011)
Parkinson's disease	It is a neurodegenerative disorder that predominantly occurs due to the malfunction of the motor nerve comprising tremor, muscular rigidity, gait abnormality, and slowness of movement. The composition of bacterial species predominantly regulates the disease. Abundance of Enterobacteriaceae results in postural instability and severity of symptoms. The metabolites produced by the gut microbiota have an essential role in the maintenance of physiological conditions of both the immune system and host	Scheperjans et al. (2015)
Major depressive disorder (MDD)	Alteration in the microbiota of the gut results in the development of major depressive disorder. It has been observed that altered microbiota is observed in patients suffering from MDD	Valles-Colomer et al. (2019) and Dinan and Cryan (2019)
Alzheimer's disease (AD)	This disease is greatly influenced by the presence of the gut microbiome. It has also been observed that the difference in the ratio of Firmicutes/Bacteroidetes forms a parallel link between AD and diabetes mellitus. It has also been observed that the different amounts of microbiota have been observed in the serum of patients suffering from AD	Zhuang et al. (2018) and Arnold et al. (2018)
Schizophrenia	Until now, a limited amount of literature is available on the relationship of microbiota with this disease, but it has been observed that males suffering from schizophrenia possess *Candida albicans* within their gut	Severance et al. (2017)
Autism spectrum disorder (ASD)	Patients suffering from this disease often observed to possess gut-associated comorbidities. Studies have shown that people suffering from ASD show marked alterations in their gut microbiota	Strati et al. (2017) and Coretti et al. (2018)

Table 5.4 Probiotics effective against various diseases and disorders

Types of disorders	Probiotics used	Effect	Reference
MDD	*Lactobacillus acidophilus*, *L. casei*, *B. bifidum*	Decrease in depression scores	Akkasheh et al. (2016)
Chronic fatigue syndrome	*L. casei*	Decrease in anxiety syndrome	Rao et al. (2009)
AD	*L. casei*, *L. acidophilus*, *L. fermentum*, *B. bifidum*	Changes in blood lipid profile and also bring about alteration in carbohydrate metabolism	Akbari et al. (2016)
HIV	*S. thermophilus*, *L. plantarum*, *B. breve*, *L. paracasei*, *L. delbrueckii*	Enhancement in neurocognitive performance	Ceccarelli et al. (2017)
Schizophrenia	*L. rhamnosus*, *B. animalis*, *B. breve*	Decrease in anxiety and depression	Okubo et al. (2019)

5.9 Conclusion and Future Aspects

The interaction among microbiome, gut, and brain plays an important role in the maintenance of the physiology and psychology of humans. Although a considerable number of researches are ongoing between gut microbiome and the CNS since the last decade, the question that persists is the relevance of pathophysiology, pathogenesis, and treatment of human brain gut disorders. But in recent times, highly controlled, large-scale, and longitudinal studies need to be performed to analyze dysbiotic gut states and various degrees of psychological illness.

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