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Review Article

Microbes-Gut-Brain Axis: A Possible Future Therapeutics Target for Gastrointestinal and Behavioral Disorder

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ABSTRACT

Gut flora or, more appropriately, gut microbiota, is an ideal example of a symbiotic relationship between prokaryotic and eukaryotic organisms. Although microbes are considered as pathogens, but gut microbiota's symbiotic co-evolution with humans over thousands of years has made it almost a virtual human organ, with unfailing existence and designated functions. Effective genetic variation of gut microbiota and their resulting metabolites has impact on host metabolism, maturation of immune system and even on behavioral development and patterns; indicating the existence of microbial-gut-brain axis. The understanding of microbial-gut-brain axis will pave the way for the researcher to develop new therapeutic strategy for the treatment of gastrointestinal disorders, metabolic disorders as well as mood and behavioral patterns.

Key word: Microbiota; Microbe-gut-brain axis; Behavioral disorder; Gastrointestinal disorder.

INTRODUCTION

The Gut-Brain interaction

The optimum functioning of the human body as a whole depends largely on the regulation and coordination among various organ systems through neural signaling or chemical messengers. Interestingly, intestinal microbiota plays an important role in maintaining interaction between two organs. [(1)] The microbes existing in the normal human intestine are ten times the total number of human body cells and they carry 150 times more genetic material than the human genome. [(2,3)] So gut microbiota behaves more like an organ, continuously modulating the functioning of gut-brain axis. Influence of gut on Central Nervous System (CNS) and *vice versa* has been recognized by scientists quite early. [(4)] The close functional relationship of the gut with the CNS can be understood by the well experienced secretion of saliva at the thought, sight or smell of certain foods and also evident from the association of intestinal distress almost consistently at times of psychological stress. Moreover gastrointestinal (GI) disorders are also shown to trigger psychological anxiety [(5-7)] and so on.

Gut brain interaction is found to be modulated by Enteric Nervous System (ENS) and chemical mediators like short

chain fatty acids (SCFA). The ENS, also known as little brain of the gut consists of little more than 100 million neurons and has its own reflex arc. [8,9] The ENS has a strategically place in brain-gut axis and extends from esophagus to anus. Digestive system is regulated intrinsically by the ENS and extrinsically by the autonomic nervous system (ANS) mainly through the vagus. 80% of vagus nerves are sensory, carrying information from gut to the CNS. [10] There are *Toll Like Receptor 4* (TLR4) on vagal sensory nerve endings which can be stimulated by *Pathogen Associated Molecular Pattern* (PAMP) recognition molecules. [11] Besides this a myriad of SCFA like Propionic acid (PPA) and Butyric acid (BA) are produced by gut microbial metabolism, which regulate the secretion of intestinal neuropeptides like the *Neuropeptide Y* (NPY). Neuropeptides and SCFA cross the blood brain barrier and has been shown to modulate CNS activity [12] in several ways. The rest 20% of vagus also known as its efferent arm, carry secretomotorfibres for vagovagal reflex regulating almost all digestion related activity i.e, gastric, pancreatic and intestinal secretions, coordinated gastrointestinal motility for propulsion of food bolus etc. [13,14] Stimulation of vagus nerve has been found by some workers to be having anti-inflammatory effect on the gut. [15] Coordination between gut and brain is maintained by these myriad of delicate and less understood signaling processes. Brain and gut interact with each other by bidirectional communication and maintains what is called as a "psycho-gastro" relation. Our mind is influenced by our gut: a "gut level feeling" in common parlance. Dysfunction of this axis triggers several pathophysiological conditions like Irritable Bowel Syndrome (IBS), Inflammatory Bowel Disorder (IBD), and anxiety. [5-7] Vagovagal reflex, hypothalamus–pituitary–adrenal axis, intestinal microbiome, Short chain fatty acid (SCFA) and Immune related factors are the various known mediators of gut-brain interaction. [10,12,16]

The roles of microbiota in human body are being explored by Human microbiome project. In the meanwhile, this review is an attempt to compile and integrate the existing knowledge and understanding on the interaction of different domains of microbiota-gut-brain axis,which may open new vistasfor treatment of the axis dysfunction,in terms of diet and lifestyle modifications or possible novel therapeutic interventions.

Intestinal Microbiota:

Coexisting among GI epithelial cell, Immune cell, 500 million neurons and an ocean of chemical mediators, the intestinal microbiota modulate human physiology, subtly but definitely. By culture independent method [17] (16S ribosomal RNA and direct sequencing of genetic material) it has been studied that human microbiota is composed of trillions of bacteria of more than 1000 different species. [2,3,18] Composition of microbiota modulates the intestinal symbiotic micro-ecosystem.

A neonate's intestine is sterile in uterus and exposed to microbes during the process of delivery. The microbiota invades and starts colonizing the growing human intestine. The mechanism of delivery (normal or cesarean) as well as exposed environment after birth has significant influence on intestinal bacterial composition. [19] Following spontaneous vaginal birth, the neonate's intestine colonizes with *bifidobacteria* and *lactobacilli* of maternal birth canal. [20] Breast feeding or formula feeding followed by solid food establishes the next stage of intestinal microbiota colonization. Breastfeeding prevents the growth of pathogenic microorganism and allows the colonization of *bifidobacteria*. Reportedly

breastfed infants' gut is more acidic as compared to formula fed infants. Intestinal microbiota composition is determined by food habits, exposed environment and host genetic makeup. [21] The role of inhabiting microbiota in human intestinal symbiotic micro-ecosystem just began to be elucidated. Recently few role of gut microbiota on human physiology has been explored by using germ free mice model, metagenomics and findings of the Human microbiome project. Gut microbiota regulate the development of gut immune system, endocrine system, gut motility and metabolism. Metabolic end products of gut microbiota are utilized by colonic epithelial cells as well as delivered to peripheral organs like liver where they modulate the different metabolic pathways. Recently by using germ free mice model and other molecular level approach, some workers reported the extended role of intestinal microbiota in neural development and in the modulation of adult behavior. [22] Role of microbiota on neural development (both structurally and functionally) add another domain to gut-brain axis which is renamed as microbiota-gut-brain axis.

Microbiota-gut-brain axis: (Microbe modulate neuro-gastrointestinal interaction)

The Enteric Nervous System (ENS) and in fact the entire enteric neuronal plexus develops from neural crest cells migrating into the bowel wall during embryonic development. ENS is a complex neural network in the gut which functions independently and modulated by autonomic input. Most of vagal fibers in gut are afferent, which carry the sensory inputs to Nucleus of the solitary tract (NTS) which in-turn transmits it to the CNS. Vagal input regulates different types of emotional and behavioral state. [22,23] *Citrobacterrodentium* infected CF-1 mice shows anxious like behavior after 7-8 h of infection along with neuronal activation in vagal ganglia. [24] Different types of neural pathway, especially vagal pathway are activated by pathogenic and non-pathogenic bacteria. [22]

Bidirectional interaction between brain and gut is maintained and modulated by neural pathways, endocrine system, and immune system as well as by differentchemical mediators like SCFA, bacteria lipopolysaccharide (LPS) and other signaling molecules. [22] Recent comparative study between germ free mice (GFM) and mice with normal microbiota throw some light on several molecular mechanisms that modulate gut-brain axis. [25] Gut microbiota have been shown to be associated with multicellular organisms from an early stage of evolution. Long term symbiotic relation between gut and microbes as well as their co-evolution, make the human microbiome indispensible for maintaining the normal physiological functions. So disturbance of human microbiome may be associated with pathophysiological conditions. [23]

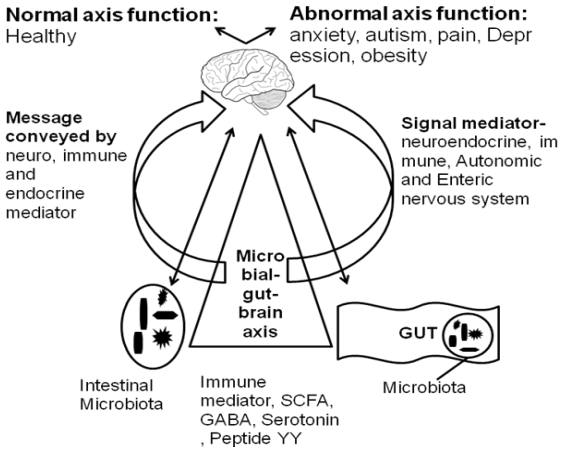

Fig. 1. Microbial-gut-brain axis and its modulators.

Microbe-gut-brain axis disorder

Experiment on germ free mice, modulation of gut microbiome by antibiotics and enteropathogenic bacterial infection prove the correlation between gastrointestinal disorders and mood

disorders. Mood disorder is common in gastrointestinal disorders like, dyspepsia and irritable bowel syndrome (IBS). Again, change in gut microbiome composition has also been reported in a few neurological conditions. Exploring gut microbes in different diseased states and understanding how gut microbes modulate the gut-brain axis may help develop a new therapeutic strategy for treatment. Different epidemiological behavioural studies on human and animal models indicate that mental disorders are closely associated with intestinal disorders.

Study of relation of Gut microbes with behavioral disorders elicited lot of interesting information. In the colon, complex carbohydrates are digested and metabolized by microbes. Several SCFA, like propionate, butyrate and acetate are generated during this process. The SCFAs apart from being a quick source of energy for colonic enterocytes, are also absorbed and transported via circulation to other organs and even to the brain by crossing the blood brain barrier. So SCFA can modulate the function of peripheral organ and CNS. Recently it has been reported that gut metabolite SCFA is associated with Autism Spectrum Disorder (ASD). [31] Remarkably 70% of autistic children have GI related syndrome including abdominal distension, pain, irritability, constipation, diarrhea and feeding problem. [26] ASD is often associated with chronic inflammatory processes like nodular lymphoid hyperplasia (NLH), enterocolitis, mucosal infiltration of immune cells in small and large intestine. [27] In ASD patient, oral non absorbable antibiotics temporarily reduce the autistic symptoms. [28] It has been reported that intracerebroventricular (ICV) infusions of enteric bacterial metabolite, propionic acid (PPA) induces ASD-like behavior in rats. [29] Studies of bacterial identification reported that subjects with ASD have different gut microbiota composition compared to normal. [30] Due to heterogenous microbiome community in ASD there is no specific trend identified yet, but it has been reported that gut microbiota and host metabolome may be associated with ASD. [31] Due to change in gut microbiota composition in ASD, the gut metabolites and SCFA like PPA may change in subjects with ASD. PPA can cross the blood brain barrier and induce ASD like behavior. [32]

On the other hand pathophysiology of irritable bowel syndrome (IBS) is considered as a disorder of complex interaction between gut and microbiota, ENS, CNS and mood disorder, which ultimately dysregulate microbial-gut-brain axis. In IBS different inflammatory mediator like Interleukins, histamine, and protease secreted from activated lymphocyte and macrophage. Increased number of CD4+ and CD8+ T cells expressing Gut homing receptor integrin β7, results in increased presence of CD8 + T cells in lamina propria and increase expression of ligand for integrin β7 in colon in IBS patients. Besides this it is also foundthat genes associated with the host defense mechanism against microbial pathogenesis also differentially expressed themselves in colonic mucosa of subjects with IBD. [33] Different inflammatory mediators, short peptides and lymphocyte act on the ENS, trigger abnormal sensory inputs in the afferent vagus, which consequently trigger aberrant secretomotor efferent vasovagal responses. ENS also regulates serotonin release, which may be disturbed in IBS. Besides this altered number of serotonin secreting enterochromaffin cells and their content in IBS also dysregulate the bidirectional gut-brain interaction. [34-37]

Symptomatic relief of IBS patient has been reported after administration of probiotics *Bifidibacteriuminfantis* 35624. [34] Compared to normal, the gut microbiome of

subjects with IBS were found to have higher levels of aerobic bacteria and decreased level of *Coliforms*, *Lactobacilli* and *Bifidobacterium.* [38-40] End product of bacterial fermentation and metabolism also regulate the sensorimotor function of gut. Remarkably treatment with probiotics relieves symptoms of different gastrointestinal disorder including IBS. [34,41]

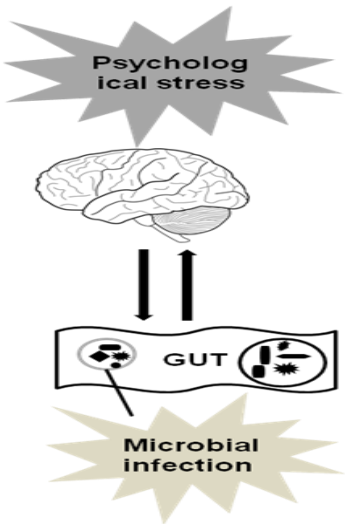

Fig. 2: Bidirectional effect of abnormal axis function.

Psychological stress is also known to be associated with IBS. In subjects with IBS viscerally painful and stressful stimuli may increase activation of anterior cingulate and in the prelimbic and infralimbic cortices. [41] Hypothalamic-Pituitary-Adrenal (HPA) axis may also get activated by different stressor in subjects with IBS, followed by glucocorticoid secretion which may alter motility, immune response, composition of gut microbiota. [34,41] Irritable bowel diseases (IBD) and co-existing anxiety and depressive disorders are also associated with gut inflammation, altered microbiota composition and dysregulation of brain-gut axis. [42]

The axis disorders associated with different psychological stressors, like small intestinal motility, migrating motor complex (MMC) altered and small intestinal transit was inhibited by removal of the stress. [43,44] Stressors can activate HPA axis and sympatho-adrenomedullary system. These systems along with serotonergic signaling are heavily involved in mood and behavior disorder in response to stress. [45,46] Psychological stress effect the intestinal microbiota composition, alter the *Bacteroidesspp*., *Clostridium spp*. in the caecum and also associated with increased number of pathogenic bacteria as well as decreased number of *Lactobacilli.* [47] Ingestion *of Lactobacillus rhamnosus* as well as cocktail of *Lactobacillus helveticus* and *B. longum* reduces anxiety and serum cortisol. [48,49] So intestinal microbiota play an important role in gut brain axis, its composition may change in different gastrointestinal disorder and different organic or functional neurological abnormalities.

Accumulating data now indicate that, the altered intestinal microbiota may even trigger obesity. The term obesity has been in our scientific lexicon for around 20 years now. Identifying the potential master regulator of obesity is of paramount importance to design the therapeutic small molecule for the possible modalities of management of obesity. Human intestine houses almost~ 10-100 trillion organism and 90% of which are Bacteroidetes, Firmicutes, and Actinobacter. Difference of gut microbiota composition between lean and obese individual has been reported by several research group. [50,51] Gut microbial diversity of obese individuals are less than that in the normal. Though it is undeniable that gut microorganisms influence obesity, but the detailed molecular and cellular mechanisms underlying it are yet to be explored. Gut microbiota regulate host immune response, energy harvesting from diet, and also regulate food intake by influencing brain-gut axis. Besides this different physiological event like feeling

hunger, satiety, food intake and energy homeostasis orchestrated by signaling molecule and vagovagal reflex between gut and brain. It has been reported that ~383 microbial genes are significantly associated with human obesity and majority of them are affect in some way human intestinal carbohydrate metabolism. [52] Several key regulator like gut metabolite (different SCFA) and gut hormones (like Peptide YY, GIP, Ghreline etc.) can cross blood-brain barrier and modulate neurological functions. [53] Further research needs to be carried out to identify the link between microbial composition of the gut as well as production and secretion of different gut metabolite and chemical mediators.

CONCLUSION

Results from different experimental and clinical studies as well as evidence from human microbiome project indicate the existence of microbe-gut-brain axis. Enormous development of sequencing technology and bioinformatics tools help researcher to explore gut microbiota population in detail by metagenomic sequencing. Identification of metabolic product of the gut microbiota just began to be elicited. And now it is being believed that the gut Microbiome is a sum of our experiences throughout our lives: the genes we inherited, the situations we faced, the hands we shook and the food we ate. It is unlikely to produce one-size-for-all solutions to modern maladies. We keep trying to unearth the intricacies of Gut-Brain cross talking with minimum effort, but biology is rarely that charitable. Therefore it is still a mystery how fine alterations of our diet, lifestyle and environment can nudge and shape the microbiota of our gut. One way of understanding the situation would be to study the gut microbiome at regular intervals and appreciate how its members flicker over time, and whether some communities are more steadfast than the others. Recently germ-free mice model enriched our understanding about the effect of gut microbiota on physiology. However the detail impact of gut microbiota and their product on gut-brain axis, immune system and metabolism are yet to be explored. Several studies indicate the association of gut microbiota with behavior and mood disorder as well as different metabolic disorders. Our microbes are truly a part of us and our personalities, and just as we are vast in our variety, so, too, are they. As gut microbiota can influence gut-brain axis and other physiological functions, altering gut microbiota composition and use of different prebiotics may be the future treatment of different metabolic, enteric and behavioral disorders, but still there is major gap in the translation of experimental research to application.

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