Gut Microbiome-A Missing Link in the Gut-Brain Axis

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The coordinated interactions between the gut and brain through gut-associated immune system, enteric nervous system (ENS), and gut-based endocrine system is now scientifically established so strongly that ENS is accepted as a separate entity and designated as gut brain or second brain, independent from the Central Nervous System (CNS)[1].The Gut-Brain axis (GBA) is a two way link between the enteric nervous system (ENS) and the central nervous system (CNS).The bidirectional communication network of GBA includes the central nervous system (CNS), both brain and spinal cord, the autonomic nervous system (ANS), the enteric nervous system (ENS) and the hypothalamo-pituitary- adrenal (HPA) axis.

However a missing link is being sighted with the advents in genome sequencing and metabolomics of gut microbiome. The discovery of gut microbiome has added a component to the complex multidirectional signaling between the gut, its microbiome, and the brain. The initial reports ofthe emerging links between gut microbiome and GBA are regarded as a paradigm shift in neuroscience with possible implications for not only conceptualization and understanding the pathophysiology of stress-related psychiatric disorders, but also their treatment.[2]

The GBA involves a complex crosstalk between neuro-immuno-endocrine mediators which monitor and integrate the emotional and cognitive centers of the brain through a complex interaction between the the Vagus nerve, Endocrine system (hypothalamic-pituitary-adrenal axis),Immune activation system, Intestinal permeability, Enteric reflex, and Entero-endocrine signaling and so on.

The human body is a small universe with a super complex ecosystem containing trillions of bacteria and other microorganisms. There is a symbiotic relationship between the human organisms and the microbiome which are reciprocally dependent on each other for survival.

In preclinical experimental set up models including germ-free animal, colonization with synthetic or human microbiota, probiotic and prebiotic administration, manipulation with antibiotics, fecal microbial transplantation, etc. have been used to study the influence of gut microbiome on the Gut-Brain axis (GBA).

In clinical practice, gut dysbiosis is associated with neuropsychiatric disorders and functional gastrointestinal disorders.In Fecal microbiota transplantation (FMT) experiments, the transplanted microbiota has been shown to transfer behavioral or disease features to the recipient animal.[3]

The bottom-up interaction of the brain by the microbiome occurs primarily through neuroimmune and neuroendocrine mechanisms involving the vagus nerve. This interaction is mediated by tryptophan metabolites, several short-chain fatty acids (SCFAs) and secondary bile acids derived from the microbial population via enterochromaffin cells (ECCs), enteroendocrine cells (EECs), and the mucosal immune cells. Signals from the Brain to the Gut Microbiota is regulated through the autonomic nervous system

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Cite this as: BMCJ 2019;5(2): 1-2

Received : 20 June 2019
Accepted : 28 june 2019

(ANS) by influencing regional functions including, secretion of gastric acid, mucus, bicarbonate, gut peptides, antimicrobial peptides, regional motility, intestinalpermeability and mucosal immune response. These ANS-induced changes in gut physiology will in turn influence the microbial habitat, thereby modulating microbiota composition and activity.[4]

Scientific information from preclinical and clinical studies related to Microbiome-Gut-brain Axis (MGBA)have shown remarkable potential for addressing not only functional gastrointestinal disorders but a wide range of psychiatric and neurologic disorders, including Parkinson's disease, autism spectrum disorders, anxiety, and depression and so on.

Different targeted approaches are under investigation or in use to address these functional, psychiatric and neurological disorders.[5]Amongst these approaches the following are to be mentioned.

- Use of antibiotic or vaccine to eliminate selected group of offending microorganisms.
- Use of probiotics, prebiotics, psychobiotics and diets to encourage the expansion of beneficial bacteria.
- Faecal microbiota transplantation (FMT) to restore necessary bacterial communities.
- Bacteriophage therapy, targeting bacterial genes to suitably modify the microbiome.
- Combination of these approaches to manipulate the whole microbiome when necessary.

Recent studies suggest that the development and function of brain are related to composition and diversity of the gut microbiota and may influence neuropsychiatric health of the host. However many issues are still to be addressed for therapeutic intervention. Nevertheless controlled manipulations of gut microbiome is a promising domain of research that may answer to some chronic functional, neuropsychiatric and degenerative disorders.

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