

A REVIEW OF GUT BRAIN AXIS- THE FOOD AND THE MOOD RELATIONSHIP

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Introduction:

The “Gut feeling” or “Butterflies in the stomach” are the common expressions that states that a communication exists between the Gut and the Brain. Gut Brain Axis refers to the two way communication between the central nervous system and the gastrointestinal system or the Enteric nervous system precisely that links the emotional and cognitive centers of the brain with peripheral intestinal functions(1). So, we can say that “*the food and the mood are interrelated.*” A troubled intestine can send signals to the brain and controls mood, behavior, sleep, appetite etc and can lead to anxiety or depression and other nervous disorders. Similarly a troubled brain can send signals to the gut and lead to abdominal cramps, diarrhea, constipation and even Irritable Bowel Syndrome (IBS)(2). The key player in these Gut Brain interactions are the *Gut Microbiota*. Recent clinical evidences have shown the role of altered gut microbiota or *Dysbiosis* in diseases like IBS, Autism spectrum diseases, Attention Deficit Hyperactive Disorders, Parkinson’s disease, Alzheimer’s disease, Multiple sclerosis, Epilepsy, Anxiety Depressive illness etc(3).

The Gut Microbiota-

In 1681 Antonie van Leeuwenhoek observed bacteria—Animalcules—first in his stool samples, and then in his saliva suggesting presence of bacteria in the gut(4). A lot of studies across centuries have been done since then. In 20th century term “probiotics” was termed by Ferdinand Vergin and its definition was approved by WHO in 2001. By the end of 20th century Ledenberg popularised the term “Microbiota” and in 21st century another new term “Microbiome” was conceptualised that refers to the 3.3 million gut microbial genes(4). Trillions of microbes including bacteria, fungi, yeast, bacteriophages and viruses inhabit

our gut which influences the development and functions of the brain along with Gut health and motility. Around 1500-5000 different species of phyla Firmicutes, Bacteroidetes, Proteobacteria and Actinobacteria comprises 99% of gut ecosystem that influences brain functions. The Gut microbiota is affected by *Diet, Stress, Infections, Antibiotics* etc. It also modulates production of inflammatory mediators like *cytokines* through Gut microbial derived metabolites like *Short chain fatty acids (SCFA- Acetate, butyrate, propionate etc), secondary bile acids and Tryptophan derived metabolites like 5-HT, Indole-3-acetic acid* and directly by producing neuroactive substances like Acetylcholine, Noradrenaline, Dopamine, GABA and serotonin etc.(5,6) Microbiota-Gut- Brain interactions occur through multiple pathways that include Neural, Endocrinal, Immunological and Metabolic pathways.

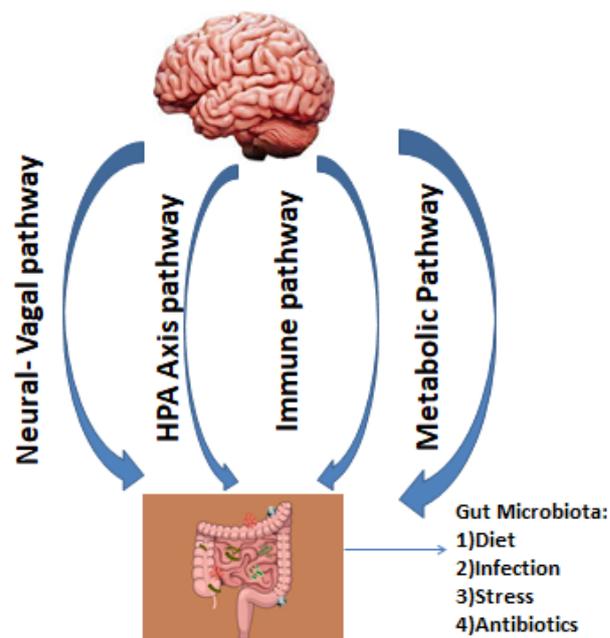
Mechanisms and Pathways of Microbiota- Gut-Brain interactions-

- 1) **Neural or Autonomic nervous system-** Both sympathetic and parasympathetic connections are present between the gut and the brain. Vagus is the main connection which sends afferent signals from gut lumen and ENS to CNS at Nucleus of Tractus Solitarius and higher centers in limbic system and brings efferent signals from brain to gut wall and ENS. This action is modulated by enteroendocrine and enterochromaffin cells via 5-HT₃ and 5-HT₄ receptors and by various gut microbe derived metabolites via Toll like receptors (TLRs)(6).
- 2) **Neuroendocrine system & Hypothalamo-Pituitary-Adrenal (HPA) Axis-** Biologically active peptides secreted from

enteroendocrine cells (EECs) in gut like *Ghrelin* and *Galanin* affects HPA axis which modulates release of ACTH/ Cortisol and norepinephrine which affects brain functions. Also various stresses leading to release of CRH affects gut mucous secretion, gastric emptying, mucosal permeability and gut microbiota. Studies suggest that mood disorders like anxiety and depression co exists with Obesity and Irritable Bowel syndrome (7). Serotonin and Dopamine also function as hormone and are modulate by Gut microbiota.

- 3) **Neuroimmune Signaling**-Gut microbes and its products like lipopolysaccharides and peptidoglycans crosses Gut barrier and Blood brain barrier to activate inflammasomes like monocytes, Dendritic cells, microglia and macrophages via Toll-Like Receptors (TLRs) and modulates synapse formation, Calcium signaling, microglial differentiation, cognition, learning, mood, memory, eating behavior etc (8). Disruption of this leads to diseases like Multiple sclerosis, Parkinson's disease, Alzheimers disease and other neuropsychiatric disorders.
- 4) **Metabolic Signaling**-The gut microbiota produces several metabolites like Short

chain Fatty Acids (SCFA), serotonin and other tryptophan metabolites that modulates the functions of both CNS and ENS. **SCFA** modulates gut motility, secretions and gut brain signaling via Free fatty Acid Receptors (FFARs) present on epithelial cells, EECs and ECCs (enterochromaffin cells), immune cells, neurons and glial cells (6). **Serotonin** produced by ECCs communicates with gut microbiota that influences 5 HT uptake and increases tryptophan in circulation that increases 5HT and other NTs in hippocampus and other regions of Brain. 5 HT via 5 HT₄ receptors modulates ENS functions. Chronic stress induced dysbiosis leads to inhibition of enzyme Dioxigenase (IDO1) that leads to conversion of tryptophan into **Kyurenine** which induces neuroinflammation and neurodegeneration. Whereas **Indoles** produced by microbial enzyme Hydroxylase has beneficial effects on gut brain homeostasis. Microbial decarboxylase derived **Tryptamine** acts via 5 HT₄ receptors and G protein coupled receptors to influence GI motility.



GUT BRAIN AXIS: Various Signaling Pathways

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