NEUROLOGICAL PERSPECTIVES OF GUT MICROBIOTA

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Abstracts

The gut microbiota comprises of bacteria, viruses, protozoa and fungi living in different districts of human body with over 70% in gastrointestinal tract. They generally live in mutually beneficial relationships in gut. It has been proved that abnormalities in composition of microbiota are often associated with presence of common metabolic diseases, type 2 diabetes and lipid disorders. Recently gut microbiota are found to be major culprits in etiopathogenesis of various neuropsychiatric disorders which are triggered by stress induced down regulation of immune system of body. The association of gut microbiota with diseases like anxiety, depression, autism, bipolar disorder, Parkinson's disease and multiple sclerosis has developed new insight in management of these diseases and advocates the need of further research in this area.

Keywords: Gut Microbiota, Immunity, Neuropsychiatry, Parkinson's disease, Multiple Sclerosis

Introduction

Holding the truth that human gut is composed of more bacteria than the number of eukaryotic cells. The human body is a super-complex ecosystem containing trillions of bacteria and other microorganisms. These microorganisms inhabit skin, mouth, sexual organs and intestines. Microbiota, an essential ecological community of symbiotic, commensal and pathogenic microorganism which share our body spaces. The co-dependency on each other in a symbiotic relationship is essential both for survival of microorganism and healthy status of its host i.e. human being. These commensal and microorganisms are vital for maintaining body haemostasis and may also be involved in etiology of several metabolic, immune and neuropsychiatric diseases. The role of microbiota is rapidly emerging in gut brain communication and alteration in composition of these gut microbiota have been observed as an important mechanism in several diseases. These micro-bacterial play a vital role in immune system maturation, digestion and absorption of macromolecules, protection of gut and also the behavioural development of an individual. A complex interplay between immune, metabolic, endocrinal and neural pathway is responsible for the protean manifestation associated with gut microflora and human body. The co-existence of stress related nervous system disorders like anxiety, depression, autism, schizophrenia, bipolar disorder and other degeneration disorders like Parkinson's and Multiple Sclerosis etc. is well established especially with gut disorders like Irritable Bowel Syndrome (IBS) &

Inflammatory Bowel Diseases (IB). The colonization of these gut microbiota starts at the time of birth and is influenced by mode of delivery, breast feeding, infection, stress, diet and in-discriminated use of antibiotics.

MECHANISM OF GUT MICROBIOTA-"STRESS BEING THE TRIGGER"

The robust data showing the correlation of stress related neuropsychiatric disorders and gut microflora is well established. Stress along with injudicious use of antimicrobials influences the microbiota and causes a diseased state. Various stress related mechanism in different disease pathophysiology can be attributed to –

1. **Dysbiosis:** The stress induced hypomotility of stomach and small intestine results in bacterial overgrowth (colonization) simultaneously with a decrease in level of beneficial Lactobacilli and Bifidobacterium. Stress also increases mucin secretion which favours the offending bacterial overgrowth.

2. **Immune activation and impairment of HPA axis:** Stress stimulates colonic stimulation and increases innate immunity via productions of cytokines by immune cells. These cytokines act on regions of central nervous system involved in HPA axis which further modifies the neuro-endocrinal activity and behavioural responses. The effect of probiotic use in clinical studies further support the linking concept of stress, immune activation and gut microflora changes in regards to gut brain axis¹. This axis acts as a two-way communication between central and gut

neurons involving gastro intestinal tract and centres of brain which are responsible for cognition and emotion.

ALTERATION IN HYPOTHALAMIC PITUITARY ADRENAL (HPA) AXIS & IMMUNE SYSTEM

The gut brain axis is composed of four major signalling pathways i.e. neural, enteroendocrinal, neurosecretory chemicals and finally immune system. In the gut mucosa associated lymphoid tissue (MALT) form the largest immune organ of human beings and comprises of more than 70% of total body immune system. The gut microbiota are vital for maturation of MALT, which triggers the innate immunity along with stimulating the local and systemic responses to attain acquired immunity. Persistent stimulation of this immune system leads to a state of persistent low grade physiological inflammation to defend against the offending pathogens². The stimulation of HPA axis via stress response leads to :-

- Release of glucocorticoids by hypothalamus
- Release of adrenaline and non-adrenaline via sympathetic branch of Autonomic Nervous System (ANS)

These products of neuroendocrine system binds the receptors on immunocytes like monocytes, macrophages, lymphocytes etc. with resultant dysregulation of cell mediated immunity (Th1 cells) & activation of Th2 cells and hence antibody production³.

LINKAGE OF GUT INFECTION AND NERVOUS SYSTEM

The mucosal lining epithelium of gut is capable of recognizing offending pathogen which results in stimulation of body host defence mechanism via macrophages, mast cells etc. The dendritic cells (which are innervated by nerve fibres from enteric ganglia, vagus and spinal visceral sensory fibres) generate signals which are responded by immune cells lying in close proximity via the cytokines⁴.

The bacterial products in form of neuroactive substances like GABA or histamine further stimulates the peripheral neurons via vagal sensory neurons and contribute to important information like the location of infection corresponding to host defence.

The central nervous system has the capacity to alter gut permeability, motility and secretion by stimulating the HPA axis, autonomic and neuroendocrine pathways which in turn can modulate gut microbial composition⁵.

GUT MICROBIOTA & NEUROPSYCHIATRIC DISEASES

Normal gut microbiota plays a vital role in the development of the brain especially with myelination process of prefrontal cortex⁶. Metabolic products of the microbial community mediates the state of health and

wellness. The various neuropsychiatric illness linked with gut microbiota are mood disorders like anxiety and depression. Absence of colonization of these microbes result in altered gene expression and turnover of various neuro-transmitters both in entral and central nervous system.

• **Role in Anxiety:** Serotonin, a neuro transmitter produced by both the brain and antero-chromaffin cells of gut is closely related to alter the mood. The host microbial interaction leads to increased plasma serotonin levels to as high as 2.8 fold. *Campylobacter jejuni*, a common gut microbe increases anxiety like behaviour by inducing C-Fos protein expression in amygdala (both central and baso-lateral nucleus), hypothalamus and Stria-terminalis. These regions of brain are involved in processing autonomic, neuroendocrinal and behavioural responses to internal changes like infections. This designs the basis of concept that the anti-depressant drugs work better with dietary modification⁷.

• **Role in Depression:** Depression is associated with stress, GI disorders like ulcerative colitis and crohn's disease which is speculated to be caused due to an imbalance between sympathetic and para sympathetic discharges from CNS. The altered gut population of *Acinetobacter* and *bacteroids* is observed in individuals with depression. It has also been suggested that the toxins liberated by these bacteria decreases the levels of neurotransmitters like 5HT and brain derived neurotrophic factors that may be responsible for depression. The increases acetate level by these altered gut microbiota also produces an overactivation of parasympathetic nervous system. This is furhter reinforced by reduced L-tryptophan levels in serum of these patients.⁸

Probiotic *Bifidobacterium* has a therapeutic beneficial effect on stress related psychiatric disease like anxiety and depression by bringing various changes in neuro transmitters, growth factors and neuro modulators. Similarly the plant aloe-vera help in increasing mucosal blood flow, intestinal mucine and bicarbonate secretion.⁹

GUT MICROBIOTA AND AUTISTIC SPECTRUM DISORDER

Autism, a neurodevelopmental disorder of early childhood is associated with deficit in social communication and imaginative development simultaneously with restricted activities, repetitive behaviour and intellectual disabilities. GI problems occur in parallel with behavioural symptom's more in autistic children.¹⁰ Apart from genetic and environmental factors, the oxidative stress and altered microbiota are also implicated in its etiology. Significant colonisation with distinct clostridial species especially *clostridium sporogens*, *clostridium tetani* and *desulfovibrio* aggravates the autism by the following mechanism-

- a) Increasing serum concentration of lipopolysaccharides;

b) Bacterial mediated production of metabolite (especially indole-3-propionic acid) induces mitochondrial dysfunction that leads to energy failure affecting brain and gut. Recent studies also highlight the role of Hyperbaric Oxygen Therapy (HBOT) to reduce the mitochondrial dysfunction, oxidative stress and an overall better outcome in the behavioural improvement and gut function of autistic children.¹¹

Treatment with Vancomycin causes substantial but transient improvement in autistic behaviour probably due to the effect of antibiotic in eliminating the neurotoxin produced by bacteria. This indicates colonisation or action of neurotoxin produced by clostridial species to play a role in autism. Further gluten free diet and probiotics also modulates the gut micro biota composition with resultant better symptom control in children with autistic spectrum disorder.

ASSOCIATION BETWEEN GUT MICROBIOTA, MYELINATION AND NEUROLOGICAL DISORDERS

Studies have shown the association of microbiome with cortical myelination. Appropriate presence of functional microbiota is essential for the correct cortical myelination especially prefrontal at well suited times of neuro development. Hence microbiota may serve as a therapeutic tool in demyelinating neurological disorders in future and help in remyelination of central nervous system.¹²

GUT MICROBIOTA AND PARKINSONISM

The severity of motor impairment is related to gastroparesis which occurs frequently in Parkinsons Disease (PD). Reduced abundance of prevotellaceae bacteria and increased abundance enterobacteria were found to be prevalent in the postural instability with gait difficulty phenotype of Parkinson disease than the tremor dominant type.¹³ Prevotellaceae bacteria are responsible for production of neuroactive Short Chain Fatty Acids and mucine synthesis by intestinal mucosa. The decreased concentration of Prevotellaceae bacteria is responsible for increasing permeability of intestine along with decrease mucin synthesis this results in miscoding of excessive expression of alpha-synuclein. These miscoded alpha – synuclein reaching to brain stem, forebrain and basal ganglion are responsible for the symptoms like bloating, constipation occurring even prior to the motor symptoms in Parkinson disease.¹⁴ PD through its gastroparesis and impaired GI motility may predispose to SIBO (Small Intestinal Bacterial Overgrowth). SIBO independently predisposes to worse motor function probably by alteration of Levodopa absorption, affecting the intestinal mucosal barrier leading to stimulation of immune system. Neural dysfunction correlated more with inflammatory response than the extent of bacterial colonisation.

H.Pylori is correlated with detrimental motor function of Parkinson disease. H. Pylori infection, causes intense neutrophilic response with resultant increased muscle contractility. Also in patients with parkinsons disease antral relaxation was higher which may be due to increased neuronal inhibition or decreased neuronal excitation. H. Pylori infection caused reduced acetyl choline (ACh) release. The more intense relaxation of antral muscle is attributed to improper cholinergic nerve function due to decrease synthesis, storage and release of acetyl choline.¹⁵

GUT MICROBIOTA AND MULTIPLE SCLEROSIS

Multiple sclerosis, an autoimmune disorder characterised by immune mediated destruction of the oligodendrocytes of the central nervous system neurons has been characterised by demyelination and axonal damage. Severe hypothetic models have been put forth to explain the auto immune trigger for this disorder and the latest and convincing model is the altered gut microbiota. In relapsing remitting multiple sclerosis (RRMS) several microorganisms like Bacteroidetes and adlercreutzia which were primarily involved in bile acid metabolism and metabolism of phytoestrogens were found to be lesser in number as compared to normal population. The metabolites of bile acid and phytoestrogens produces an intense anti-inflammatory response which may be responsible for autoimmune etiology in RRMS.¹⁶ Some of the other neurological disorders associated with altered gut brain axis are stroke, alzheimer's dementia where researches are still going on to understand the etiology in relation to gut microbiota.

TARGETING THE MICROBIOTA: MODULATION BY DIET

The most effective way to modulate the composition of gut microbiota is through a balanced diet. This balanced diet comprises of meat, fish, fruits, cereals, legumes, vegetables and olive-oil (commonly known as Mediterranean Diet). This diet is most efficient to promote optimal gut microbiota composition. This diet benefits by restoring intestinal permeability, reducing endotoxins and its related consequences to gut brain axis with an overall positive metabolic effect. Therefore a healthy lifestyle based on this diet as foundation, is probably the best way to prevent and treat different disorders associated with disturbances in gut microbiota.

Conclusion

Gut microbiota has a significant impact on the brain development along with myelination process. This review focuses on the influence of gun microbiota on diseases concerned with the central nervous system such as depression, autism, Parkinsonism, demyelination diseases and other psychiatric diseases associated with socio-cognitive deficits. The present review points towards the institution of probiotics or aloe vera, as an alternative

strategy along with judicious use of antibiotics which will help to maintain a perfect balance in gut microflora. This intern throws light on the speculation of extending the therapeutic benefits of antibiotics from short term to long term treatment of autism spectrum disorder. Therefore this review advocates the need for further research in this area with the perception; that the harmony in the gut microbiota would enable to improve the treatment of neuropsychiatric diseases from bench to the bedside.

References

1. Ghosh, Amit, et al. "Microbes-Gut-Brain Axis: A Possible Future Therapeutics Target for Gastrointestinal and Behavioural Disorder." *International Journal of Health Sciences and Research* 2015; 5.1:321-29.
2. Galley, Jeffrey D., and Michael T.Bailey. "Impact of stressor exposure on the interplay between commensal microbiota and host inflammation." *Gut Microbes* 2014;5.3:390-396.
3. Padgett, David A., and Ronald Glaser. "How stress influences the immune response." *Trends in Immunology* 2003; 24.8:444-448.
4. Smith, Peter Andrey. "The tantalizing links between gut microbes and the brain." *Nature* 2015; 526:312-314."
5. Mayer, Emeran A. "Gut Feeling: The Emerging Biology of Gut-brain Communication." *Nature reviews. Neuroscience* 2011; 12.8:10.1038/nrn3071.
6. Hoban, A.E., et al. "Regulation of prefrontal cortex myelination by the microbiota." *Translational Psychiatry* 2016;6.4:e774.
7. Goehler, Lisa E., et al. "Campylobacter jejuni infection increases anxiety-like behaviour in the holeboard: possible anatomical substrates for viscerosensory modulation of exploratory behaviour." *Brain, Behaviour and Immunity* 2008; 22.3:354-366.
8. Jagmag, Shail Adrian, et. Al. "Exploring the Relationship between Gut Microbiome and Depression." *Trends Gastroenterol* 2016; 1.001.
9. Desbonnet, L., et al. "Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression." *Neuroscience* 2010; 170.4:1179-1188.
10. Mangiola, Francesca, et al. "Gut microbiota in autism and mood disorders." *World Journal of Gastroenterology* 2016; 22.1:361.
11. Parracho, Helena MRT, et al. "Differences between the gut microbiota of children with autism spectrum disorders and that of healthy children." *Journal of Medical Microbiology* 2005; 54.10:987-991.
12. Mayer, Emeran A., et al. "Gut microbes and the brain: paradigm shift in neuroscience." *The Journal of Neuroscience* 2014; 34.46:15490-15496
13. Agata Mulak, Bruno Bonaz. Brain-gut-microbiota axis in Parkinson's disease. *World J Gastroenterol* 2015; 21:10609-10620.
14. Bercik Premysl, et al. "Immune-mediated neural dysfunction in a murine model of chronic Helicobacter pylori infection. " *Gastroenterology* 2002; 123.4:1205-1215.
15. Parmar, Arpit. "Gut-brain axis, psychobiotics and mental health." *Asian Journal of Psychiatry* 2016; 22:84-85.
16. Jun Chen, Nicholas Chia. Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. www.nature.com/ScientificReports |6:28484 | DOI: 10.1038/srep28484.