

PSYCHONEUROGASTROENTEROLOGY- A REVIEW OF CURRENT UNDERSTANDING

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ABSTRACT

The existence of a gastrointestinal (GI) nervous system distinct from the CNS has been recognized for more than a century. With impressive brain-like features, the GI nervous system is increasingly being postulated to have an indispensable role in the pathophysiology of various neuropsychiatric disorders. Recent research has disproved the earlier notion of the communication between the higher brain and the GI brain being a unidirectional one. The major evolutionary event of microbial colonization of the GI tract in mammals has also contributed to the complexity of the GI-brain communication, and the GI microbiome has been hypothesized to explain the genome-complexity conundrum in humans. The role of the secretory products and the genetic components, for example Pre/Pro-biotics derived from various microbial species, are becoming the focus of intense research. Though psychoneurogastroenterology is a nascent entity, the evidences accumulated over the past decade definitely indicate an enormous potential for the exploitation of the GI-brain interactions, especially in neuropsychiatric research. This review about the developments in this field is aimed at igniting more research interest into this relatively neglected field, with the hope that it may open the door to innumerable future possibilities in neuropsychiatry.

Keywords: psychoneurogastroenterology, enteric nervous system, gut microbes, probiotics.

INTRODUCTION

Years ago somebody said, “the best way to a man’s heart is through his stomach”. Though it was not the interpretation of any clinical research in the past, looking at it from the current perspective proves that it indeed has got a testable scientific basis in the emerging field of psychoneurogastroenterology.

Though the enteric nervous system (ENS) had been a neglected field of research till recently, the remarkable discovery made by Michael Gershon that 90% of the body’s serotonin is located within the walls of the gastrointestinal (GI) tract ignited interests of various neuroscientists, including psychiatrists, about the GI nervous system.¹

THE ENTERIC NERVOUS SYSTEM

It is considered as a single entity comprising of a network of neuronal plexuses like the Meissners and Auerbach’s plexus, surrounded by a pool of more than 30 neurotransmitters like serotonin, dopamine, glutamate, norepinephrine and nitric oxide, and other chemical mediators like neuropeptides and enkephalins. It also contains glia-like supportive cells, and together contains nearly 100 million neurons as that in the spinal cord.^{2,3} Though the ENS is considered to have an independent activity, it is very much under the control of the CNS. The neural control of the gut has four levels of integrated organization based on a hierarchy. The first level is

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constituted by the ENS which has its own independent functioning. The second level in the hierarchy is the modulating role of the pre-vertebral sympathetic ganglia. The third level is constituted by the sympathetic and parasympathetic outflows arising from the CNS. The higher brain centres which provides inputs to the sympathetic and parasympathetic systems comprises the level 4, at the top of the hierarchy.³

Earlier it was considered that the higher brain (CNS) had complete and unidirectional influence over the ENS, but current research and experiences propose that the gut may also influence the higher brain, hence making it a bidirectional interaction.³

According to the developmental biologists like Dr David Wingate, the earlier organisms, especially the tubular organisms which stuck to rock surfaces to allow food to pass through them, had only an abdominal neuronal system. But, as living organisms evolved and the challenges for maintaining and sustaining life increased in the form of increased need for nutrition and other basic life processes like reproduction, the 'reptile brain' or limbic system evolved to cater to those higher needs. It is believed that, like the CNS neuron, the ENS too originates from the neural crest cells. Gershon proposed that the body maintained the enteric or GI brain as a separate entity in higher animals, and this local mini brain later got connected to the higher brain via the vagus nerve.⁴

THE FIELD OF NEUROGASTROENTEROLOGY: THE BRAIN CHILD OF MICHAEL GERSHON

The 1998 hot-seller "The Second Brain: A Ground-breaking New Understanding of Nervous Disorders of the Stomach and Intestine" by Gershon proposed a new branch of medicine named Neurogastroenterology which encompasses the study of the brain, the gut, and their interactions with relevance to the understanding and management of GI motility and functional GI disorders.¹

It is a well-known fact that the gut can upset the brain, just as the brain can upset the gut. A high prevalence of various psychiatric comorbidities seen with various gastrointestinal disorders may stand testimony to that. A lot of research has been done to identify a common etiopathogenetic basis for GI and psychiatric disorders.

INFLAMMATORY BOWEL DISORDERS AND PSYCHIATRY

Inflammatory bowel disorders (IBD) like Crohn's disease and ulcerative colitis have a high prevalence of comorbid mood and anxiety disorders and even personality changes. There is evidence that anxiety and depression symptoms are more severe during periods of active disease. The few studies that address the issue of anxiety and depression as risk factors for IBD do not yet provide enough information to support definite conclusions. There is evidence, however, that the course of the disease is worse in depressed patients. The chosen treatment modality may also have behavioural complications, as with corticosteroids inducing mood disorders or other psychiatric symptoms.⁵

IRRITABLE BOWEL SYNDROME AND PSYCHIATRY

The brain-gut interactions are increasingly recognized as potential underlying etiopathogenetic models for the functional gastrointestinal disorders like Irritable Bowel Syndrome (IBS). It is known that various physiological and pathological changes influencing the CNS and ENS stimulate the brain-gut axis by involving the neural pathways and the immunological and endocrinological mechanisms. Animal models have shown that such influences can affect modulation of various GI functions like motility, secretion and immune functions via different levels of neural control, including CNS functions related to perception and emotional response to visceral events. Regarding the evaluation of the role of psychological stress, experimental animal models report a consistent pattern of GI motor alterations 1) delaying gastric emptying and 2) accelerating colonic transit in

response to various psychological and physical stressors. It is proposed that this differential modulation of gastric motility is mediated by the endogenous corticotropin-releasing factor (CRF) via activation of CRF receptors in the brain. The endogenous serotonin, peripherally released in response to stress, has also been considered to have a role in stress- and central CRF-induced stimulation of colonic motility by acting on the 5HT-3 receptors. The brain substrates which mediate these changes have been linked to structures which regulate emotional changes, like the amygdala.⁶ The significant influence of psychological stressors and psychosocial factors on the symptom profile of IBS may lead us to the proposal for a biopsychosocial model for IBS like for various other psychiatric disorders. An association with psychosocial stressors may be supported by the high prevalence of anxiety spectrum conditions like panic disorder, generalized anxiety disorder, social phobia, dysthymia and major depression in IBS patients.⁶

MICROBIAL COLONISATION

The microbial colonisation of mammals is considered to be an important evolutionary event. It is significant in the context of the GI system, as nearly 95 percent of the human microbiota is present in the GI tract. Mainly comprised of commensal (symbiotic) microbial organisms and referred to as the microbiome, it serves an adjunctive role in several physiological functions like nutrition, digestion, neurotrophism, inflammation, growth, and immunity. It is postulated that nearly 1000 species of bacteria are present, accounting to a total number of nearly 100 trillion organisms with a density more than any known microbial system.⁷ Such a complex microbiome is hypothesized to play a significant role in the regulation of multiple neuro-chemical and neuro-metabolic pathways with the help of a complex mechanism of highly interactive and symbiotic host-microbiome signalling systems.⁸ This is evidenced by the presence of the small noncoding RNA and micro RNA of microbiomal origin in the signalling cascades in the GI tract and

also in the systemic and lymphatic circulation around the CNS.^{9,10,11} The studies in germ-free mice have also indicated the role of the microbiome in the normal development of the physiological functioning of the ENS.⁸

HUMAN BIOCHEMICAL OR GENETIC INDIVIDUALITY: POTENTIAL ROLE OF THE MICROBIOME

Through the findings of the Human Genome Project, it is now accepted that the human genome comprises of nearly 26,600 protein encoding transcripts which lead to a very complex phenotypic expression. But the rice genome *Oryza sativa*, with nearly 46,000 functional genes, has a very simplistic phenotypic expression.^{12,13} What could explain this diversity? It is postulated that the 1000 species of bacteria contribute around 4 million genetic transcripts which, when combined with the host genome, adds up to more than 4,026,000 genes which can possibly explain the genome complexity conundrum.^{12,14,15}

The potential for the human microbiome to play a role in the etiopathogenesis of various psychiatric disorders is being increasingly identified, based on certain observations made by researchers as follows:

1. The bacterial species *Lactobacillus* and other *Bifidobacterium* species are capable of metabolizing glutamate to GABA, a key mediator in anxiety disorders.^{16,17,18} A recent randomized controlled trial had demonstrated the anxiolytic properties of probiotics *L. helveticus* and *B. longum* in humans with anxiety disorders.¹⁹
2. BDNF, an important neurotrophic factor, is reported to have a reduced expression in patients with schizophrenia or depressive illness. Similar deficiency of BDNF has also been demonstrated in the cortex and hippocampus of germ-free mice.^{18,20,21} Whether the role of the microbiome in the expression of BDNF may be significant in genesis of psychological morbidity seem to be

promising in the search for the cause of certain psychiatric disorders.

3. β -N-methylamino-L-alanine (BMAA), an amino acid found in certain bacteria, which helps the organism in forming its structural compounds and in resisting host immunity, is elevated in the brains of patients with Amyotrophic Lateral Sclerosis, Parkinson-dementia complex of Guam, or Alzheimer's dementia. It is known to be a neurotoxic amino acid, as it has been found to be detrimental to the functioning of the NMDA glutamate receptors via its glutathione depleting and oxidative stress inducing properties. BMAA has been hypothesised to originate from the cyanobacterium, a member of the human microbiome.²²
4. Stress has been found to produce changes in the constitution of the GI microbiome and may have a potential role in elevating similar neurotoxins and lead to cognitive dysfunction.^{15,23}
5. Researchers have proposed autoimmune and infective theories for the etiopathogenesis of various psychiatric disorders like schizophrenia, depression, obsessive compulsive disorder and autistic spectrum disorders. The most plausible underlying phenomenon is considered to be the molecular mimicry initiated by exposure to certain strains of Streptococci in the GI tract and the cross reactivity with the mitochondria. Mitochondria are believed to have originated from bacteria via endosymbiotic relationships that formed very early in the evolutionary history of eukaryotes and hence the potential for molecular mimicry (a mechanism by which infectious agents or other exogenous substances may trigger an immune response against auto-antigens due to similar immunological profiles). It is suggested that differences in exposure and genetic vulnerability toward human microbiota-mediated autoimmunity may be significant determinants in the etiopathogenesis.^{17,24,25,26} Two conditions hypothesized to emerge due to an infective origin are PANDAS and OCD.

6. The co-occurrence of GI disorders with autism spectrum disorders (ASD) is widespread. Studies have reported that the number of GI symptoms can be directly proportional to the severity of autism.²⁷ The composition of the bacterial flora in autism patients was found to have predominance of Bacteroidetes compared to Firmicutes which are predominant in normal controls.²⁸ Also, it is speculated that certain bacterial neurotoxins, especially the one produced by Clostridia, may worsen the behavioral symptoms in ASD.²⁹ Studies have reported that short term treatment with antibiotics can ameliorate behavioral symptoms in some cases of ASD.³⁰ Probiotics are under research for their efficacy in treating certain behavioral symptoms in ASD.

PROBIOTICS AND PSYCHIATRY

Probiotics are live microorganisms which, when administered in adequate amounts, confer a health benefit on the host. Although in existence for more than a century, research data on the efficacy of probiotics have been available only recently. Initially studied by Russian biologist Ilya Metchnikoff in 1907, there is increasing interest about the positive effects of the microbiome/probiotics toward the CNS via neural, neuroendocrine, neuroimmune and humoral links.^{31,32} Current research on probiotics is mainly in the field of cognitive disorders, multiple sclerosis, ASD, depression, anxiety and schizophrenia. One double blinded randomised controlled trial had attempted to reproduce, in adult human volunteers, the positive effects of the probiotics *L. helveticus* and *B. longum* previously observed in an animal model. The trial reported that active treatment with probiotics reduced psychological distress in humans, and a concomitant reduction of urinary cortisol was observed.³³ This again proves that the bacteria, in the form of positive probiotics, may hold promise in treating various behavioural problems.

SO WHAT IS PSYCHONEUROGASTROENTEROLOGY?

Psychoneurogastroenterology is a concept which evolved from neurogastroenterology and encompasses the study of the brain, the gut, and their interactions with relevance to the understanding and management of GI motility and functional GI disorders. Psychoneurogastroenterology may be described as a field which seeks to identify and describe the relationship of various neuropsychiatric disorders with other GI disorders, and also the potential influence of the GI nervous system and its associated microbiome in the etiopathogenetic mechanisms of neuropsychiatric disorders.

FUTURE POSSIBILITIES

The field of psychoneurogastroenterology is in its infancy. It appears to be a promising area of research for developing various diagnostic and therapeutic strategies for psychiatric and cognitive disorders. Some of the future possibilities as elucidated by Dr. H. Nasrallah are:

- 1) To identify and quantify neurotransmitter presence in the GI tract, which may help in identifying deficiency states as in Parkinson's disease and Alzheimer's dementia, which may allow an earlier diagnosis, much before CNS changes become evident.
- 2) Considering GI biopsy to identify neurotransmitter abnormalities in conditions like schizophrenia.
- 3) Devising strategies to modulate the ENS and thus, indirectly, the neurotransmitter levels in the CNS.
- 4) Altering the composition of the vast GI microbiome to promote positive health and cognitive effects via the use of prebiotics and probiotics, and may be as an adjunct to psychotropic medications.³⁴

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