Role of Gut Microbiota in Major Depressive Disorders: A review

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ABSTRACT

Major Depressive Disorder (MDD), the fourth leading cause of disability, affects 350 million people globally and shares genetic overlap with psychiatric disorders like bipolar disorder and schizophrenia. Research suggests MDD is linked to increased levels of pro-inflammatory cytokines, including interleukin, indicating immune system involvement. Gut microbiota (GM) plays a crucial role in regulating the gut-brain axis, and gut dysbiosis can disrupt this axis, leading to the production of harmful metabolites, immune mediators, and pro-inflammatory cytokines. This negatively impacts neurotransmitter production, such as norepinephrine, serotonin (5-HT), and dopamine, all essential in mood regulation. Non-pharmacological approaches, including ketogenic diets, calorie restriction, and intermittent fasting, have been shown to protect and restore GM by improving intestinal barrier integrity and stimulating cell regeneration. A healthy GM strengthens tight junctions and encourages antimicrobial peptide production. Additionally, probiotics downregulate stress-induced 'GABA' mRNA expression in the amygdala and prefrontal cortex, reducing corticosterone levels. This helps prevent gut leakage, reverses stress-induced HPA axis activation, and shows promise in minimizing depressive thoughts and behaviors.

Introduction

MDD is a devastating disease having complex and multidimensional manifestations and is widely distributed in populations with substantial symptom severity and impairment of day-to-day work. According to the Global Burden of Disease research, depression is regarded as the fourth most common cause of disability, with approximately 350 million people being affected implicating a significant impact on public health. The average lifetime prevalence of MDD in European nations was found to be 11.32 per cent, while the average 12-month prevalence was found to be 5.2 per cent.[1]

Various possible pathophysiological mechanism of MDD involves boosted levels of the pro-inflammatory cytokine interleukin IL-6, acute phase C-reactive protein (CRP), malfunction of the glucocorticoid receptor with hyperactivity of the HPA-axis and lower levels of vitamin D. [2,3] Frequently unrecognized and underdiagnosed, Major depressive disorders are challenging to treat. Unemployment, poor socio-economic status, chronic/life-threatening disease, sexual and physical abuse, psychological neglect and negative family environment, domestic violence exposure, and separation of children from parents due to death or divorce are predominant stressful events and risk factors related to MDD.[1,3] Disorders, such as bipolar and schizophrenia disorders genetically overlap with MDD. Previous meta-analyses indicate elevated cortisol levels with MDD in patients with involvement of the HPA axis in patients with MDD.[2,3] Long-term treatment with a synthetic glucocorticoid is connected with a higher risk for MDD, suicide and other severe neuropsychiatric disorders.[4-6]

Psychotherapy and pharmacotherapy using monoaminergic antidepressants are two major verticals and first-line agents for the management of MDD. Various guidelines conclude that therapy should be used to treat moderate-to-severe depression episodes with combination therapy. Even when combined, psychosocial treatments and conventional pharmaceuticals for depression are only successful in roughly 74% of patients. More than 30% of patients do not respond to monoaminergic antidepressants which lately results in relapse indicating other biological mechanism underlying MDD. One of the frequent hypotheses is the impairment of gut and brain communication, resulting in disorders of gut-brain interaction which was earlier known as functional gastrointestinal disorders.[7] Abnormal eating habits have a negative influence on the physical or mental health of the patient. Human–microbe symbiosis extends the significant benefit to human mental health, and several evidence also supports the hypothesis of communicating in both directions among the gut and brain axis.[8,9] In recent years, environmental exposures and an unhealthy diet have influenced the gut microbial composition which are highly associated with the increased incidence of depression. Antibiotics also play a crucial role in the subsequent development of depression due to the reduction in the diversity of the gut microbiota.[10-13] The gut microbiota and the host have a symbiotic connection that is controlled by a complex network of interactions, including metabolic, immunological, and neuroendocrine crosstalk. Through a number of channels, including nerves, the HPA axis, and the immune system, the gut-brain axis links the brain and gut. Depression is likely the result of a dysfunctional brain-gut axis caused by factors like psychological stress and diseases that affect one or more brain-gut axis pathways.[14] It was reported that through humoral and neural pathways the gut microbiota can influence behavior and brain activity and also have treatment for neuropsychiatric disorders.[15-19]

Chronic stress disrupts the gut microbiota as well as the mind and the stress response system. [20,21] Analysis of genes of gut microbes through recent developments in metagenomics has attained tremendous importance in the field of gut microbiota over the last decade. After weaning, nutrition has a substantial impact on the gut microbiota; bad diets drastically disrupt the microbiome and raise the prevalence of depression. Existing research studies reveal that

the use of probiotics, prebiotics and a healthy diet can help in recovering the gut microbiota that will help in improving gut-brain axis function which would play an important role in the treatment of mental illnesses including depression.[22]

Gut microbiota and the gut-brain axis

Microbiota refers to diverse populations of microorganisms present in the body's various ecosystems. 'Gut microbiota' refers to a diverse array of bacteria, archaea, helminth parasites, protozoa and eukarya colonising the GI tract which is estimated to exceed 10^{14} bacterial cells. Gut microbes confer various benefits and are key to many aspects of human health including immunity, metabolism and neurobehavioural traits. Predominantly bacteria from 3 major phyla including Actinobacteria, Bacteroides, and Firmicutes are present in diverse gastrointestinal microbiota.[23] The study demonstrated that the gut-brain signaling via the vagus nerve, in combination with oral treatment with Lactobacillus rhamnosus JB-1, could mediate anxiolytic and antidepressive-like effects.[24] These microorganisms harbour 50-100-fold more genes leading to functional expansion of the host genome. These genes code for several enzymes and proteins which in turn play an essential role in improving host metabolism & regulation of host physiology. Earlier research concluded that defects in brain processes which is a brain-centric perspective were solely responsible for the development of mental illness without considering the impact of the metabolic and immune systems of the body on the development and complex functions of the brain. Various studies have reported that the key regulator of the gut-brain axis is gut microbiota. Diverse microorganisms residing in the human gut referred to as gut microbiota (GM) has the ability to produce various metabolites along with immunological and neurochemical factors in the gut which ultimately has a significant impact on the nervous system.[25,26]

Various functionally important metabolites are produced by GM including bile acids, catecholamines, Short chain fatty acids (SCFAs) like acetic acid, butyric acid, isovaleric acid, isobutyric acid etc and lipopolysaccharides (LPS). In addition to metabolites various neurotransmitters including histamine, dopamine, 5 HT, melatonin, glutamate and gama amino butyric acid (GABA) and hormones including cholecystokinin, glucagon-like peptide-1, leptin and ghrelin are produced by GM which significantly interacts with CNS and enteric nervous system (ENS).[27]

A complex communication exists between the gut and brain which ensure appropriate maintenance of gastrointestinal homeostasis with multiple effects on cognitive functions. Various intestinal functions including gastric reflex, gastro-endocrine signalling and immune activation are monitored and integrated through the gut-brain axis via neuro-immuno-endocrine mediators. CNS, ANS, spinal cord, brain, and HPA (hypothalamic pituitary adrenal) axis mediate this bidirectional communication network.[28] There is evidence that specific gut microbiota play an important role in the modulation of tryptophan into various metabolites, including kynurenine, indoles, and tryptamine, among others. The metabolites of tryptophan can act on the CNS through vagal afferents or through neuroendocrine mechanisms.[29-32] It was also reported that the intricate connection between diet, the gut, and certain gut microbes, and brain diseases by investigating how gut microbes interact with dietary tryptophan, which produces a number of neuroactive metabolites implicated in several brain disorders.[33] HPA axis is a part of the limbic system which is a stress-efferent axis responsible for mediating responses towards stress through hypothalamic secretion of the corticotropin-releasing factor (CRF). Corticotropin-releasing factor (CRF) stimulates the secretion of corticotropin from the pituitary which intern stimulates cortisol release which is a major stress hormone from the

adrenal gland which, in turn, influences gastric effector cells, immune cells, epithelial cells, gastric neurons and smooth muscle cells. Patients with acute-stress paradigms have been found to be associated with increased intestinal permeability and elevated levels of cortisol which implicates mucosal inflammation and alteration of gut functions.[34] Chronic activation of HPA due to gut dysbiosis in turn activates systemic inflammatory pathways which leads to an increase in the synthesis of reactive oxygen species (ROS) and reactive nitrogen species (RNS). Elevated levels of RNS and ROS cause substantial damage to DNA and proteins in mitochondria with elevated levels of malondialdehyde and 4-hydroxynonenal, by-products of lipid peroxidation observed in depressed patients. Endogenous antioxidants including melatonin, glutathione, and glutathione peroxidase play a protective role in mitochondrial functions and regulation of cAMP/circadian genes. Stress-induced elevated levels of ROS and RNS reduce levels of endogenous antioxidation dysregulating cAMP/circadian genes and modifying behavioural patterns.[35]

Gut microbiota improves metabolic efficiency conferring better metabolism of amino acids, polysaccharides, micronutrients and xenobiotics which was detected through analysis of 16S rRNA and metagenomic sequencing of Human faecal samples.[36] Fermentation of the majority of the soluble dietary fibre (SDF) and unabsorbed starch is through Gut microbiota directing to the establishment of SCFAs such as butyrate, propionate, acetate & pentanoate which contributes 70 per cent of the production of ATP in epithelial cell proliferation, colon, and activation of G-protein–coupled cell surface receptors 41 (GPR41) and 43. These GPR43 and GPR41 regulates the balance of microglia cytes affecting affect brain-gut axis activity. SCFAs are also found to stimulate the production of serotonin through gut endocrine cells which is a predominant monoamine neurotransmitter with a significant part in the regulation of anxiety/depression development and normal mood.[37] Any disturbance in intestinal microbes disrupts the release of monoamine neurotransmitters including serotonin, dopamine, γ-aminobutyric acid and histamine leading to disturbance in the stability of the HPA axis. The irritable bowel syndrome (IBS) is often considered the prototypical gut-brain disease due to its sensitivity to probiotics.[38] Altered gut microbiota causes irritable bowel syndrome (IBS) with an elevated postprandial level of serotonin in plasma and was found to be associated with depressive symptoms and anxiety trait.[39,40] SFAs can penetrate the blood-brain barrier and are also involved in the production of neurotransmitters including norepinephrine and 5-HT. Neurotransmitters, their metabolites and SFAs modulate various immune system pathways and intestinal permeability which also influences behaviour, memory, learning, locomotion, and neurodegenerative disorders. Hence any changes in the composition of microbiota lead to changes in neural activity and brain which are well assessed by magnetic resonance imaging.[41] Anila studies have shown that gut microbiota causes dysregulation of HPA axis leading to a reduced level of 5-HIAA, norepinephrine, and 5-HT in the depressed mice' hypothalamus with the presence of differential bacteria taxa in the mice gut.[42,43]

Patients with depression are associated with low-diversity dysbiosis including reduced levels of Lactobacillus, Faecalibacterium, Firmicutes, Bifidobacterium, and Ruminococcus phyla, while levels of Bacteroides, Provotella, and Proteobacteria get elevated levels. This leads to altered microbiota increasing stress which in turn causes hyperactivity of the HPA axis halting the release of cortisol.[44] The most widely used tool for the assessment of the interaction of intestinal microbes with brain function and behaviour is found to be germ-free (GF) mice. Stool transplantation from patients with gut dysbiosis in the gut of germ-free (GF) mice discloses the interaction of gut microbiota with animals' behaviour through the microbiota-gut-brain axis.[45]

Gut microbiota and Immune system

Epithelial cells of the gastrointestinal (GI) tract composed of a single layer of different intestinal epithelial cells that act as a major line of defence providing a physical barrier for pathogens working in coordination with immune and stromal cells. Various peptides such as lysozyme C, alpha-defensins, C-type lectin, and phospholipases are produced by Paneth, Goblet, and enteroendocrine cells with anti-microbial properties. Development of regulatory T cells is promoted through the translocation of luminal antigen-presenting cells to CD103C dendritic cells which serve as a defence mechanism. Junction adhesion molecules comprising occludins, claudins, and zonula occludens act as intestinal barrier machinery simultaneously regulating the permeability of the gut. LP-lymphocytes, Peyer's patches, and intraepithelial lymphocytes are lymphoid tissues present in the gut that constitutes an adaptive immune system and it helps to the protection of the intestinal barrier via releasing immunoglobulins.[46] Experimental studies on germ-free animals suggest that for optimum development of the immune system microbiota colonization is a crucial stage. In case of poor microbiota colonization gut mucosal immunity remains underdeveloped with the presence of small payer patches and lymph nodes accompanied by decreased numbers of immune cells such as CD4+LP T-cells, IgA-producing plasma cells, and intraepithelial αβ T-cell receptor CD8+ cells which compromises gut immunity.[47]

Gut dysbiosis and leaky gut frequently trigger stress which triggers the immune system via the HPA axis causing increased release of pro-inflammatory cytokines including IL-6, IL-1 beta, sIL-2R, IL-18, interferon-gamma (INF-γ), and CRP. A significant correlation exists between depression and degenerative, inflammatory, genetic, and functional with the bidirectional association between cytokines and behavioural alterations.[48] Patients with gut dysbiosis had elevated blood circulating biomarkers including protein zonulin, lipopolysaccharide (LPS) endotoxins, gut inflammatory proteins, Lipopolysaccharide-binding protein (LBP) and sCD14 indicating compromised intestinal barrier.[49] Binding of LPS with sCD14 in the cell wall of gram (-ve) bacteria stimulates the release of pro-inflammatory cytokines triggering adaptive immune response mediated through IgA- and IgM antibodies. This systemic inflammation due to translocation of commensal gram(-ve) bacteria due to improved intestinal permeability with triggered cytokinin-mediated immune response had been a role play in depressive patients.[50] LPS is crucial for the activation of the toll-like receptor (TLR)-4, which in turn promotes the nucleotide-binding oligomerization domain-containing proteins (NBODPs)-1 and/or -2, which has additional effects on depression. Increased gut permeability due to gut barrier dysfunction causes translocation of LPS from the gut to the brain leading to blood-brain barrier dysfunction with a further negative effect on brain functions.[51]

Gut Microbiota and Depression

The research suggests a connection between gut microflora and depression. Any changes in gut microbiota composition may increase microbial lipopolysaccharide production which leads to inflammatory response activation. The inflammation and depression work like a vicious cycle. The inflammation may cause depression and depression decreases cytokines responses which ultimately leads to inflammation.[52] The vagus nerve receives the signal from cytokines which is responsible for behavioural effects due to the linking between the vagus nerve and the hypothalamic-pituitary-adrenal axis.[53] The relation between composition and diversity of the fecal microbiome was investigated, employing 1,054 participants from the Rotterdam Study cohort with depressive disorders, and validated the results in 1,539 subjects in the Amsterdam HELIUS cohort. The association of thirteen microbial taxa, including genera Subdoligranulum,

Lachnoclostridium, Eggerthella, Sellimonas, Hungatella, Ruminococcaceae (UCG002, UCG003 and UCG005), Coprococcus, LachnospiraceaeUCG001, Ruminococcusgauvreauiigroup, Eubacterium ventriosum and family Ruminococcaceae with depressive symptoms was identified. Several important neurotransmitters for depression are made by these bacteria, including butyrate, glutamate, gamma amino butyric acid (GABA), and serotonin.[54] Microbial flora can be used to control the working and development of HPA axis which is responsible for depression. The disturbance in microbial flora can lead to dysregulation of HPA axis which causes depression. Clinical studies explain depression by activating the kynurenine pathway. The activation of the kynurenine pathway is due to gastrointestinal tract inflammation which causes neuroinflammation. It also affects the production of various neurotransmitters through the neurotransmission process.[55] In recent years it has been noted that microbiomes play important role in depression.[56] The person should have stable microbial flora to avoid neurological disorders. The choice of diet and lack of exercise can worsen the condition in microbial flora causing depression. The diet routinely consumed in western countries can disturb the microbial flora which can induce depression. High-fat-content food can also induce inflammation which leads to depression.[57] The correct number of probiotics can reduce depression and anxiety by managing microbial flora. The major factor for dysbiosis is a sedentary lifestyle. The exercise can help maintain the balance between pathogenic gut flora and beneficial microbiota.[58] The relationship between GM and exercise is not clear. Disturbance in sleep or lack of sleep may trigger depressive symptoms. A sound sleep of 7-9 hours is an ideal recommendation for adults to maintain microbiota balance and lack of depression.[59] It is essential to accurately identify changes in featured microbes that occur in individuals with mental disorders because there may be significant differences in the composition of their gut microbiome among individuals to provide personalized mental disorder treatment through the targeting of gut microbiota.[60]

The levels and spread of potent pro-inflammatory endotoxin named lipopolysaccharide are affected by dysbiosis which leads to a change in intestinal permeability. Lipopolysaccharide plays a major role in the modulation of the central nervous system.[61] The activity of the amygdala affecting the areas of emotionalism is changed due to increasing levels of endotoxin. The brain activity is affected by increasing levels of cytokines which alters neuropeptide synthesis. The altered levels of cortisone also affect anxiety levels.[62-63] It is also seen that neuropsychiatric parameters like sleep, mood and appetite are affected by intestinal microbiota secreted neuroactive molecules. The many kinds of neurotransmitters like acetylcholine can be secreted by lactobacillus subspecies which can regulate mood, memory and learning abilities. The anxiety caused by increasing levels of cortisone can be inhibited by intestinal microbiota through HPA axis.[64] Brain-derived Neurotropic factor (BDNF) production and activity play a major role in mood disorders. The administration of antibiotics and probiotics like oligo-saccharide and galactic-saccharide can increase the levels of BDNF in the hippocampus and periphery. It becomes clear that modulating complex behaviours such as social ability and anxiety in person is seen due to an imbalance between gut bacteria and the CNS.[65] Few of the short-chain fatty acids metabolized by gut bacteria have an impact on the neuroactive properties of the person. The imbalance in gut microbiota can also cause the alteration of stress hormones corticotropin-releasing factor (CRF) and cortisol. It is also seen that gut microbiota can change human behaviour by acting with personality traits.[66-67] Due to changes in gut microbiota, it is also observed that a person's hunger is decreased and preference for healthier food is relatively increased which is due to a change in neural response towards food.[68] Numerous Neurotransmitters like serotonin and melatonin concentration in the body is dependent on the regulation and amount of amino acids which are regulated by gut microbiota.[69] Researchers have shown that Selective Serotonin Reuptake Inhibitors exert their therapeutic effects via the

vagus nerve. This provides further evidence that the vagus nerve plays an important role in maintaining beneficial microbiota in the gut.[70] The gut-brain axis is implicated not only in depression, but also in reactions to vertically during pregnancy, psychiatric drugs, autism, and several other diseases.[71-72] Evidences that GM can affect homeostatic emotions which indirectly affects a person's mood or energy levels. The various regions of the brain are in constant communication with internal organs most importantly with the gut so the microbiota can send the signals to the brain for cognition, memory and mood by regulation of various metabolites.[73] The multidirectional relationship is established between gut microbiota and the central nervous system still the exact mechanism needs to be established for the effect of microbiota on mood.

Conclusion

MDD is a debilitating disorder characterized by depression, anorexia, negative thinking, insomnia and in severe cases suicidal thoughts. The co-relation between the microbiota and key depression can be illuminated through the Mendelian Randomization. A positive correlation has been established in various studies between gut dysbiosis and depression as gut dysbiosis is an important risk factor in the development of MDD and more severe cases of mental illness. The composition of gut microbiome may also leads to depression. Gut dysbiosis causes dysregulation of the gut-brain axis which in turn increases the production and release of toxic metabolites, immune mediators and proinflammatory cytokines. It also has a negative impact on the production of neurotransmitters including norepinephrine, 5-HT, and dopamine which plays a significant role in depressive illness.

Proper care and restoration of GM through non-pharmacological approaches like ketogenic diets, calorie restriction, and intermittent fasting improves the integrity of the intestinal epithelial barrier and stimulates the regeneration of intestinal cells through the production of mucin and raised levels of SCFAs. Balanced and healthy GM promotes the synthesis of antimicrobial peptides by epithelial cells and reinforces tight junctions. Supplementations with probiotics downregulate stressed-induced GABA Aα2mRNA expression in the prefrontal amygdala and cortex which in turn reduces corticosterone levels. It also prevents gut leakage with the reversal of stress-induced HPA axis activation and has shown promising results in minimizing negative thoughts and behaviour. In order to identify and comprehend the crucial role of gut microbiota, and to build the understanding of its importance, larger and more carefully designed studies are required. Further research is necessary to understand the interactions between gut microbiota, diet and disease.

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