The gut-brain connection: A qualitative review of the conceptualisation and implications of the gut-brain-microbiome axis

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Abstract

Current research shows that the gastro-intestinal and central nervous systems are linked by multiple interconnecting layers and have been known to continually influence each other's actions. The enteric nervous system, vagus, hypothalamic pituitary axis, and the local endocrine system are few of the components of this complex system, forming neurological, immunological as well as endocrine bridges through which information relay occurs. In addition, the gut microbiota exerts overarching influence on all these components, directly and indirectly affecting the brain and impacting human behaviour. This, in effect, creates a gut-brain-microbiotal (GBM) axis, which has a potential role in various physiological functions. It is also implicated in pathological processes as well, and is found to have a role in many psychiatric conditions such as autism spectrum disorders, schizophrenia, mood disorders, substance use and neurodegenerative disorders. The mechanisms involved in each disorder, as well as psychological correlates of the GBM axis, along with potential treatment implications involving microbiota and possible strategies to modulate microbiota to affect changes in psychiatric symptoms are explored in this article.

Keywords: Gut-Brain Axis, Gut microbiota, Gut-Brain Microbiota Axis in psychiatric disorders, Psychobiotics.

Introduction

The human gastro-intestinal system contains the enteric nervous system, which consists of the myenteric and mucosal plexuses which are acted upon by the sympathetic and parasympathetic limbs of the autonomic nervous system, with the hypothalamic-pituitary-adrenal axis playing a major role. The vagus is the major parasympathetic supply and effects changes in the central nervous system (CNS) in response to changes in the gut environment. It is also influenced by the local endocrine system which produces various hormones which act on the gut wall, as well as cross the blood brain barrier (BBB) and modulate CNS functioning. Physiologically, these involve pathways between cognitive and emotional centres of the brain and peripheral intestinal functions. The state of the gut influences the state of the mind, and much evidence points to behavioural alterations brought about by this gut brain axis.[1] The human gut also contains various commensals, termed the microbiota, which share a symbiotic relationship with the host. The human gut microbiota has been referred to as the 'forgotten organ', owing to the different effects it exerts on the host, and humans as Super-organisms, whose metabolism represents an amalgamation of the efforts of both host and microbiota.[2] The microbiota thus interact with various physiological systems and result in modification of many biological functions as well as outward behaviour, forming a Gut-Brain Microbiotal (GBM) axis, which has been found to be involved in the pathophysiology of multiple psychiatric illnesses.

Historical perspectives

Hippocrates, in 460 BC, put forth the idea that all disease begins in the gut.[3] William Beaumont, an American Army Surgeon, made various observations of the functioning of the GI system in vivo, which earned him the title, Father of Gastric Physiology. He observed that there were changes in the composition of gastric secretions and bile associated with emotions like anger or fear.[4] Around the same time, interest in the effects human microbiota have on human health and disease began, and the term 'intestinal toxemia' were used to describe a process whereby intestinally derived toxins could influence systemic health. Ilya Miecznikov theorised that ageing is a consequence of toxic bacteria in the gut, in his work, *The Prolongation of Life: Optimistic Studies*, where he wrote of the potential life lengthening effects of the lactic acid, proposing a diet containing fermented milk, which contained bacilli which produced a large amount of lactic acid.[5] Dr. George Porter Philips, in the early 1900s, described melancholia as a condition of auto-intoxication, where there was defective alimentation, constipation and an overall clogging of the metabolic processes. He reported that consuming a gelatine-whey formula containing live lactic acid bacteria improved depressive symptoms in adults with melancholia.[6] Dr. Henry Cotton, an American psychiatrist postulated that mental illness was a consequence of infection, based on the observation that patients with high fever sometimes developed odd behaviours and started hallucinating. He believed that teeth were the most likely location of infection, conducting thousands of tooth extractions, and when this did not work, he resorted to removing tonsils, sinuses, gall bladders, testicles, ovaries, stomachs and colons, all of which were suspected to house infections, calling this, *'Surgical Bacteriology'*, and most had high mortality rates, considering this was in the pre-antibiotic era.[7]

More recently, research on microbiota in influencing brain and behaviour has created an offshoot of interest. That

the microbiota may form part of the gut-brain-axis as an intermediate or a distinct nodal entity by extension of the axis needs further exploration. Nonetheless, its involvement is undeniable, and presently, research is being conducted at a furious pace to delineate and better conceptualise these effects in detail.

Components of the gut-brain axis
The neural connections

This consists of the enteric nervous system (ENS), vagus, spinal nerves and HPA axis. The ENS formed by the myenteric and submucosal plexus constitutes the largest nervous system outside the CNS, often referred to as a 'second brain', as it is capable of functioning after complete autonomic denervation, but is usually under tight control of the autonomic nervous systems.[8] The vagus is the principal component of the parasympathetic nervous system with afferents distributed to all layers of the digestive wall, but not crossing the epithelial layer and not in direct contact with luminal content. Its activation depends on chemical signals such as peptide hormones, cytokines, metabolites and neuroactive molecules. Information travels through the vagus to the cortex through relay stations, like the nucleus tractus solitarius (NTS), nodose ganglion, then to hypothalamus and the limbic system. Descending projections subsequently take the same pathway to reach the gut wall layers.[1,8] [Fig. 1]
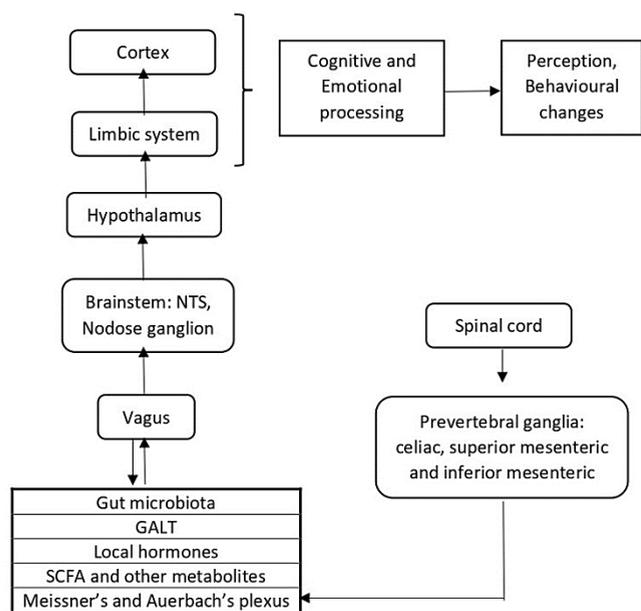

Fig. 1: Neural pathways in the GBM axis

The endocrine system

Stressors, both physical and psychological, can act on amygdala and hippocampus, thus activating the hypothalamus to produce corticotrophin releasing factor (CRF). The CRF acts on anterior pituitary adrenocorticotrophs to stimulate production of adrenocorticotrophic hormone (ACTH), which brings about cortisol production.[9] The ENS contains CRF ligands and

receptors, with CRFR1 widespread in colon and CRFR2 prevalent in upper GI tract, and implicated in ion secretion causing paracellular permeability dysfunction leading to microbial invasion and mucosal inflammation, the stress-induced nature of recruitment of receptors leading to heightened stress susceptibility.[10]

Locally, there are a set of specialised endocrine cells called Entero-Endocrine cells (EECs). They sense fermented bacterial products, which act on the G-protein coupled receptor expressed on the luminal surface, which activates the cell to produce peptide YY (PYY), neuropeptide Y (NPY), cholecystokinin, glucagon-like peptide (GLP)-1 and 2, and substance P, which act on gut as well as CNS.[11] [Fig. 2]
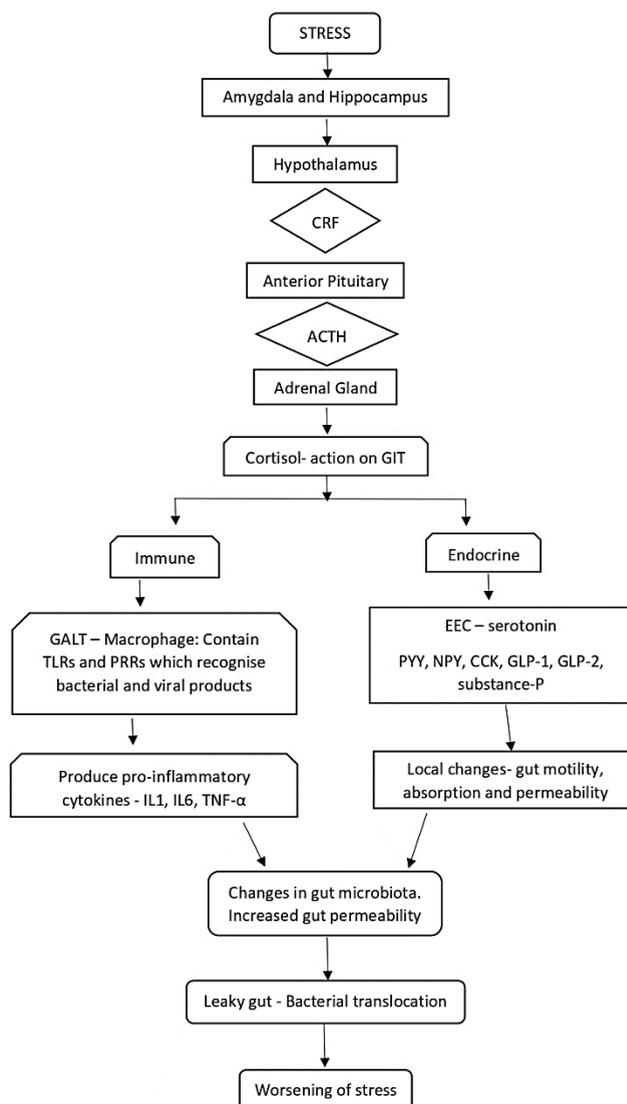

Fig. 2: Endocrine and immune pathways in the GBM axis

The immune system

The Gut Associated Lymphoid Tissue comprises 70% of the body's immune system. The Toll Like Receptors (TLR) recognise bacterial and viral components and mount

immune responses through pro-inflammatory cytokines, and are even found on neurons, which respond to microbial products.[12] Depression is associated with increase in inflammatory markers like IL-6, tumour necrosis factor (TNF) - α, and C-reactive protein (CRP), which activate the Immune Inflammatory Oxidative and Nitrosative (IONS) pathway, leading to lipid, protein and DNA damage, increasing gut permeability. The increased nitric oxide and inducible nitric oxide synthase products cross the blood brain barrier (BBB) and cause neuroinflammation associated with major depressive disorder.[13] [Fig. 2]

The leaky gut hypothesis

Depression has been associated with low grade inflammation, causing loss of integrity of tight junctions, which increases permeability and lead to bacterial translocation and peripheral immune activation.[14]

Short chain fatty acids (SCFA)

SCFAs namely acetic acid, butyric acid and propionic acid have been implicated in regulating the sympathetic nervous system, histone acetylation and methylation, mucosal serotonin release and secretion of intestinal peptides like GLP-1, PYY and CCK, decrease BBB permeability, promote CNS angiogenesis and neurogenesis, therefore influencing host metabolism, nutrition and emotional regulation.[15] G-protein receptor-41 (GPR41) is expressed in ENS as well as in sympathetic ganglia, vagal, dorsal root and trigeminal ganglia and is used by SCFAs to bring about these effects.[16]

The gut microbiota

The human gastro-intestinal tract alone contains around 10^{14} microorganisms, which includes around 1000 species and >7000 strains of bacteria, the most predominant phyla being bacteriodes and fermicutes.[17] Others like proteobacteria, fusobacteria and actinobacteria are present in relatively lower abundance.[18] Human beings have a variation of three distinct patterns of gut microbial composition, called enterotypes. Enterotype-1 has a majority of Bacteriodes, with Prevotella and Ruminococcus similarly constituting enterotypes 2 and 3 respectively. This composition was thought to be at least partially genetically mediated, but it has been found that there are similarities in gut microbial composition in unrelated individuals sharing a household, thus pointing to the role of diet and environment.[19] The genome of these microbes is called the Microbiome, and the human gut microbiome contains 150 times more genes than the human genome.[17] However, there is an extensive identifiable Core Microbiome, at the genetic rather than the organisational level, and deviations are associated with different physiological states. The Human Microbiome Project is helming further research into delineating the transcriptome (genes involved in protein production), the proteome (the set of proteins produced by the microbiota) as well as the metabolome (the group of metabolic substances produced) of the microbiota.[20]

The gut-brain-microbiota axis

Germ free (GF) animals have been found to have impaired development of ENS and CNS, with neurotransmitter expression altered in both systems, all this reversed with microbial colonisation.[21]

Gut microbiota can regulate circulating pro-inflammatory and anti-inflammatory cytokines and maintain homeostasis at the intestinal epithelium, and certain probiotics have been found to restore tight junction integrity in animal stress models, along with attenuating HPA axis and autonomic nervous system activities. Dysbiosis (imbalance in the gut microbial community associated with disease) may increase the production of proteases and lead to increased immune responses resulting in chronic gut inflammation.[22] Hsiao and colleagues noted that Bacteroides fragilis corrected intestinal permeability defects in mouse models, by altering tight junction expression, cytokine production and correction of dysbiosis noted in GF mice.[23]

Tryptophan is converted to serotonin and kynurenine, and microbiota can modify the kynurenine arm of tryptophan metabolism. Tryptophan 2, 3- dioxygenase (TDO) and Indoleamine 2, 3-doixygenase (IDO) catalyse the rate limiting step in the production of kynurenine and these enzymes can be induced by inflammatory cytokines and microbes, by modifying this have been found to alter the concentration of kynurenine thereby decreasing the availability of circulating tryptophan.[24] Gut derived serotonin cannot cross the BBB, and therefore, reduction in the amount of tryptophan available for crossing the BBB will result in decreased concentration of serotonin in CNS, leading to depressive symptoms. Amino acid transporters are present in bacterial cell wall, through which histidine and glutamate enter and are converted to histamine and GABA. Microbiota also modulate the endocannabinoid receptor concentration in gut epithelium. Serotonin, melatonin, acetylcholine, nitric oxide, nor-epinephrine and dopamine are also synthesised by different strains. [Table 1] [25-27]

Enterochromaffin cells (ECC) act as an important hub in the bidirectional GBM transmission. In addition to producing around 95% of the body's serotonin, they are polymodal chemo sensors, containing receptors responsive to inflammatory and bacterial metabolites (SCFA, bile acids, taste receptors, TLRs) on the luminal side, and are synaptically connected to vagal afferents and postganglionic sympathetic nerves, besides having a close association with immune cells in the gut wall. This results in the ECCs being a pivotal interconnecting entity within the CNS- ENS-HPA-immune-microbiotal network.[28]

Table 1: Neurotransmiters produced by gut microbiota.[35-37]

Gut Bacteria	Neurotransmitters produced
Lactobacillus and Bifidobacterium	GABA from monosodium glutamate
Escherichia coli, Bacillus and Saccharomyces	Norepinephrine
Streptococcus, Escherichia and Enterococcus	Serotonin
Escherichia, Serratia, Lactococcus	Dopamine
Lactobacillus acidophilus	Increases the expression of cannabinoid receptors in the brainstem
Numerous Strains	Short Chain Fatty Acids
Lactobacillus plantarum	Acetylcholine
Streptococcus, Lactobacillus, Citrobacter	Histamine

Table 2: Methods of investigating the GBM axis: Strategies utilised to delineate the effects of microbiota on the host functions, can be divided into five types.[39]

Method	Description
Germ free studies	1. GF mice are used to observe effects of absence of microbiota on CNS development and other host functions 2. Most studies use gnotobiotic mice (where the entire microbial palette is either known or excluded).
Infection studies	1. GF animals can be inoculated with specific strains individually or sequentially 2. To assess specific post inoculation changes in the host as well as microbe-microbe interactions.
Faecal transplantation studies	1. Observation of specific functions of human GBM system by transplanting human microbiota into GF mice
Probiotic and antibiotic studies	1. To study effects of microbiota altering agents including prebiotic substances and even diet patterns.
Human studies	1. Intrapersonal variation in microbiotal composition is considerably lesser than interpersonal variation means that each individual would represent his or her own best control for assessing effects of perturbations in composition on body functions 2. Family or individuals living together would provide the next best controls.

Table 3: Questions pertinent to psychological correlates.

Social, cultural and Developmental psychology	1. What is the role of the gut microbiota in psychological development? 2. Are there critical windows or sensitive periods for development of microbiota similar to the development of psychological functions such as language? 3. Are psychological & microbial development impacted by similar perinatal factors? 4. How does the composition and function of the microbiota impact upon social behaviour? 5. Does social interaction impact upon the microbiota? 6. How does culture interact with the presentation and treatment of disorders of the brain–gut–microbiota axis?
Clinical psychology	1. Can interventions designed to target psychological well-being alter the microbiota? 2. Can interventions that ameliorate or reduce dysregulation of the microbiota improve psychological well-being? 3. Among the prevailing psychological interventions mindfulness-based therapies represents a promising intervention for tackling chronic stress especially in a near prototypical gut brain disorder such as IBS. Could MBSR or MBCT have an influence on Gut Microbiota?

Adapted and modified from Allen et al, 2016

GBM axis in stress

Stress increases sympathetic activity, which increases bacterial permeability, increases circulating IL-6 and monocyte chemotactic protein-1 (MCP-1) and intestinal IgA, as well as pro-inflammatory gene expression, leading to modification of microbial profile and increase virulent strains, leading to dysbiosis.[29] Maternal separation in rodents causes long lasting hyperactivity of HPA axis, anxiety like behaviour, visceral hypersensitivity, altered cholinergic activity in gut and increased intestinal permeability. GF maternally separated mice do not show any different behaviour compared to control GF mice, thereby necessitating the premise that gut microbiota are essential for expression of anxiety like behaviour.[30] Knowles et al investigated the impact of psychological stress on GI flora under everyday stressful conditions and found lactobacilli to be significantly low during the high stress conditions.[31]

Role of GBM in psychiatric illness
Autism spectrum disorders (ASD)

The presence of GI disturbances in children with ASD is well documented, with diarrhoea and constipation being the most common, in addition to belching/vomiting, abdominal discomfort, gastritis, gastro-oesophageal reflux disease, lactose intolerance, malabsorption.[32] A possible association of autism with celiac disease was considered as some studies have pointed to higher frequency or family history of celiac disease and elevated anti-gliadin antibodies in ASD. Lau et al tested for potential association of celiac disease or gluten sensitivity with autism. They compared IgG and IgA antibodies against gliadin in children with autism, unaffected siblings and unrelated unaffected controls. They found the IgG antibodies were significantly higher in autistic children as compared to the two control groups, with no difference observed in IgA levels. In addition, antibodies to deamidated gliadin and transglutaminase-2 did not differ, and association between increased IgG and HLA DQ2/DQ8 was not observed, and it was concluded that such individuals may have a non-celiac gluten sensitivity, and not celiac disease per se. Strikingly, this study had two control groups. It suggested the possibility of using these as biomarkers, and that the unique antibody response to particular gluten molecules would be associated with specific HLA genes.[33] Another link with autism and GI disease comes with zonulin, a haptoglobin-2 precursor protein which increases spaces between gut epithelial cells. Zonulin has been implicated in increasing gut permeability and dysbiosis. The gene for zonulin is present on chromosome-16, which is the high risk ASD chromosome. One study found that zonulin was increased in ASD. It may provide a link between autism and gut dysbiosis as well as a possible role as a potential biomarker in a set of ASD patients.[34] It has also been noted that children with ASD have had a history of using significantly more antibiotics than healthy controls. They have also been found to have abnormal colonisation, possibly due to higher use of antibiotics and restricted diet.[35] LPS component of cell wall

of gram negative bacteria have been noted to be higher in ASD, and inversely correlated with socialisation scores on Vineland Adaptive Behaviour Scale and Autism Diagnostic Interview Revised (ADI-R) domain-A score.[36] Supplementation of Bacteroides fragilis has been shown to reduce gut permeability, alter microbiotal composition and reduce ASD like behaviours.[37] Therefore a causal association between use of antibiotics in pregnancy and ASD in the offspring needs to be further explored. Wang et al noted that ASD patients had a higher concentration of SCFAs and ammonia in faecal matter.[38] It has been hypothesised that SCFAs could play a critical role in ASD pathogenesis. SCFAs, especially propionic acid has been implicated in crossing BBB and inducing autistic behaviours like hyperactivity and repetitive behaviours in animal studies.[39]

Attention deficit hyperactivity disorders (ADHD)

Gut microbiota have been known to participate in mediating food allergies, and children with food allergies and asthma often have higher rates of co-morbid ADHD.[40] Pärtty et al found that increase in Bifidobacterium in infancy predicted ADHD and Asperger's syndrome, and that probiotic supplementation in infancy may prevent neuropsychiatric manifestations.[41] A meta-analysis reported that there was a reliable effect linking the Kaiser-Permanente diet (eliminating salicilates, artificial food colours and flavours, and the preservative butylatedhydroxytoulene) to ADHD symptoms.[42] These studies have led to popularity of multiple different diets among individuals with ADHD in the quest to find non-pharmacological methods to control symptoms.

Schizophrenia

Multiple evidences linking schizophrenic symptoms to perturbations in body immunity, most often originating the gut which may lead to neuro-inflammation have been proposed. Buscaino conducted a post-mortem study with 82 schizophrenia patients, and found that 50% had gastritis, 88% had enteritis and 92% had colitis.[43] Severance et al showed that anti Saccharomyces cereviseae antibodies (ASCA) were elevated in schizophrenic patients, Higher food antigen antibody levels correlated with GI inflammation only in schizophrenic group, raising the possibility that inflammation was a part of the disease itself.[44] Schizophrenia patients have higher rates of formation of immune complements C1q with food antigens, and increased casein IgG antibody in individuals with already high levels of C1q was predictive of 18% increased risk of schizophrenia.[45] Soluble CD14 (sCD14) and lipopolysaccharide binding protein (LBP), markers of bacterial translocation, were measured in individuals with schizophrenia, bipolar disorder and non-psychiatric controls, along with antipsychotic naive and treated individuals. Patients with schizophrenia had increased sCD14 and LBP, which correlated with increase in C-reactive protein (CRP), thus pointing to a common pathway of inflammation. LBP significantly correlated with body mass index scores,

suggesting that these inflammation patterns may be responsible for the high co-morbidity of schizophrenia with cardiovascular disease, diabetes and cancer.[46] Beumer et al have reported that schizophrenia and other psychoses are associated with abnormal monocyte and macrophage activation, leading to hyperactivity in the innate immune system.[47]

Minocycline has been found to improve negative symptoms as well as exert beneficial effects in treatment resistant schizophrenia. This is thought to be due to it resulting in shift from autoimmune TH17 to anti-inflammatory TH2 responses.[48] Experiments on rat schizophrenia models have shown that treatment with Bacteroides fragilis leads to improved gut microbiotal composition, decreased permeability and decreased anxiety like symptoms. In addition gut microbiota also have interactions with psychotropic medication, as olanzapine has been found to modify microbiota composition and trigger inflammatory responses, thereby suggesting that antipsychotics use the microbiotal pathway to effect weight gain and other metabolic complications in rat models. Evidence to this is further strengthened by resolution of these symptoms by administration of antimicrobials.[49]

Mood disorders

Much evidence, both direct and indirect, has been found, linking gut microbiota to mood changes. Park and colleagues used olfactory bulbectomy to induce depression and anxiety like behaviours in mice, and found that bulbectomised mice had increased central CRH expression and increased expression of c-fos gene, serotonin and motility in the colon, as well as altered microbial profile.[50] Zheng et al showed that depressed patients and normal controls had significantly different gut microbiota, and that GF mice transplanted with microbiota from depressed patients showed depression like symptoms, whereas GF mice with 'normal' microbiota did not show such behaviour. The microbial genes and host metabolic products, especially amino acids and carbohydrates considerably differed in mice with 'depression microbiota' and those with normal microbiota.[51] Wong et al compared normal mice with mice genetically deficient in or pharmacologically inactivated caspase-1, and noted that caspse-1 deficient mice had decreased depressive and anxiety like behaviours, associated with increase in Akkermansia, which attenuates inflammation and Blautia, which rebalances gut microbiota.[52] A meta-analysis by Hannestad et al showed that treatment with SSRIs resulted in decreased IL-1β and IL-6 levels with improvement in depressive symptoms.[53]

Alcohol use disorders

Alcohol use causes long standing changes in eating habits, as ethanol forms the major source of caloric intake in alcohol dependent individuals. These dietary changes lead to changes in the gut microbiota. Leclercq et al examined the gut microbiota of alcohol dependent (AD) subjects and found that 40% of them had abnormal gut microbiota, and

had much more severe levels of depression, anxiety and craving compared to the AD subjects without dysbiosis. Even at the end of detoxification (18 days), dysbiotic AD patients continued to have these symptoms, whereas those without dysbiosis recovered completely. They noted that dysbiosis was associated with high intestinal permeability, and higher abundance of Lachnospiraceae, Blautia and Megashpaera, along with decrease in Ruminococcaceae and Clostridia. They suggested that dysbiosis and high permeability could be potential targets for management of alcohol use disorders, by targeting the negative reinforcers of drinking, viz., depression, anxiety and craving.[54] Vagal afferents relay in the NTS, projects on to the Central Nucleus of Amygdala, and has anti-inflammatory activity in normal state. Neurons with GLP-1 and glutamate activity project on to the amygdala and mediate pro-inflammatory responses by activating CRF neurons, which may be one of the pathways involved in alcohol withdrawal leading to neuroinflammation. These changes manifest in case of sudden alterations in compensatory mechanisms, as neuroinflammation is at a lower level in chronic alcohol exposure, when compared to controls.[55]

Neurodegenerative disorders

Recent studies have demonstrated links between changes in gut microbiota and biomarkers of Alzheimer's disease. Vogt et al compared the composition of the gut microbiota in participants with and without Alzheimer's dementia and found that the gut microbiota of the patient group had reduced diversity and a distinct composition compared to controls, with a decrease in fermicutes, which had primarily been associated with type 2 diabetes mellitus and obesity, suggesting that microbiota induced insulin resistance could worsen the neurodegeneration.[56] Willette et al found increased bacteroides and decreased bifidobacterium, resulting in a pro-inflammatory phenotype, as bacteroides are known to increase bacterial translocation and bifidobacterium leading to increased LPS translocation in Alzheimer's individuals, with LPS found to increase Aβ peptide assembly by increasing its toxicity, and called a pathological chaperone.[57]

Cattaneo and colleagues also found gut microbial modifications in cognitively impaired older adults (without Alzheimer's diagnosis), and found that Escherichia/Shigella was increased and the anti-inflammatory microbe Eubacterium rectale decreased in individuals with presence of amyloid deposition on PET imaging compared to those who did not show presence of amyloid.[58] Evidence of the role of gut microbiota in influencing cerebral amyloidosis is provided by Harach et al, who showed that GF transgenic Alzheimer's mice showed lesser cerebral amyloid deposition than conventional Alzheimer's model mice. Bacterial amyloids are produced to enhance adhesion, biofilm formation, invasion and thereby virulence. These can influence human neurodegeneration by interacting with host proteins and cross-seeding of neural protein, leading to enhanced misfolding or accelerating nucleation.[59]

A probiotic study by Akbari et al showed that Bifidobacterium given in patients with severe dementia showed improved mini-mental state examination (MMSE) scores after 12 weeks of probiotic treatment.[60] Long term broad spectrum antibiotic treatment in mice has been shown to decrease Aβ plaque deposition, with alteration of cytokine signatures and attenuated plaque localised glial reactivity. This study particularly made note of the increase in CCL-11 (C-C motif chemokine ligand-11), which has previously been associated with hippocampal neurogenesis and whose gene cluster has been implicated as a risk factor for late onset Alzheimer's.[61]

Psychobiotics
'Encephalobiotics' is the term given to prebiotics, microbes or microbial parts which influence the microbiome to affect cognition and mental well-being. Dinan and colleagues have defined 'Psychobiotics' as live organisms that, when ingested in adequate amounts, produce health benefits in patient's suffering from psychiatric illness. They are a type of probiotic, which are defined as live microorganisms, which when administered in adequate amounts confer a health benefit to the host.[62] They act by multiple pathways to exert effects on the CNS by decreasing the HPA activity. Microbiota influence the metabolism of neuroactive substances and sometimes even alter the expression of neurotransmitter receptors in different brain regions. For instance, Rosseaux et al found that L. rhamnosus treated animals showed alteration in GABAB1b mRNA, with increased expression in cortical regions and decreased expression in hippocampus, amygdala and locus ceruleus, which were dependent on vagus, as vagotomised mice did not show these changes.[63]

Akkasheh et al reported significantly decreased Beck's depression inventory scores in patients with major depressive disorder who received probiotics compared to patients who did not.[64] Another study conducted by Steenbergen and colleagues found that multispecies probiotic supplementation decreased cognitive reactivity to sad mood and had decreased rumination, suggesting that probiotics could potentially improve depressive cognition.[65] Messaoudi et al found that Lactobacillus helveticus and Bifidobacterium longus containing probiotic decreased depression, anxiety, level of somatisation, psychological distress and even 24-hour urinary cortisol in healthy human volunteers.[66]

Limitations of using psychobiotics for treatment of psychiatric illnesses
Most studies have used combination of strains, which makes it difficult to delineate a one-to-one cause effect relationship for individual strains. There are no approved guidelines for dosage or duration of treatment as of yet, which may be species and also host dependent. Different studies define symptoms and outcomes differently, making it difficult to reach a viable conclusion. Although stigma associated with the use of psychotropics may be bypassed using over the counter probiotics, there has been no consensus regarding the use of probiotics as an alternative or adjuvant treatment in psychiatric disorders.[67]

The psychological correlates of GBM axis
Microbiota can modify cognitive performance, susceptibility to stress, anxiety behaviour, pain perception and sensitivity, sickness behaviour, and even social behaviour. The physiological response to microbiota is tied up with an emotional response, which would in turn impact on the gut as well. Temperament and character may be transmitted between subjects, through fetal microbiotal transmission. High neuroticism and low conscientiousness are associated with increased proteobacteria in the gut.[68] The lifestyle, diet and healthcare changes have led to perturbations of the gut microbiota and as a possible consequence, human behaviour. We still do not have definitive evidence regarding whether psychological interventions can influence gut physiology and the gut microbiota. Translational applications from lab models to human psychology can lead to potential behavioural interventions targeting a healthy diet, thereby resulting in positive psychological effects, as psychological interventions may impact significantly upon microbial composition through top down regulation. Understanding psychology in the context of the GBM axis involves the physiological, intrapersonal, interpersonal and social and cultural levels. A few key questions pertinent to the psychology of the gut brain axis that warrants further longitudinal research has been summarized in Table 3.

Implications
With further experimentation, investigations which use microbes or their products or antibodies as biomarkers of various diseases may be designed. Current experimental research has extensive data from which probiotic strain selection for different conditions may be guided. Strains that specifically target the physiological changes seen in psychiatric illnesses, such as those which lower the LPS burden, oxidative stress, proinflammatory cytokines, intestinal permeability and uremic toxin burden, and those that have beneficial influence on stress resiliency, mood, cognition and those that alter neurotransmitter levels would be good targets. The multiple pathways involved in leading to a particular outcome in the GBM axis functioning, and the close overlap between relationships may lead to an ambiguity between correlation and causation. The changes in symptoms with change in microbiota that have been seen in studies may turn out to be co-incidences rather than direct causative associations, and further studies with more stringent study designs may well fail to demonstrate these changes. Most studies so far have been hypothesis generating and not definitive, and do not answer the question of whether gut dysfunction precedes behavioural alteration or vice versa, and connecting the Human Microbiome Project with the Human Connectome Project may give us an insight into these questions.

Conclusions

The 20th century was ruled by antibiotics, with all microbes being deemed harmful. The 21st century brought with it the understanding that microbes have beneficial effects on health, and the possibility of manipulating them for management and prevention of various diseases is being explored, the current stand being that the state of gut would markedly affect the state of mind. The utility of probiotics is questionable as it is as of yet not regulated by the FDA, and it is vital to underscore the fact that any discussion of probiotics as intervention is not akin to a discussion of psychotropic medications. If the now warranted clinical translation of animal data into human intervention studies do reveal a future role of probiotics in mental health relevant to clinicians, it would most possibly be as an adjuvant to well established front line care with psychotropic medications and psychotherapy.

Conflict of interest

None

Permissions

Not applicable

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