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Gut microbiota and psychiatric disorders

Abstract

The impact of gut microbiota in mental health has been one of the most exciting and probably one of the most discussed topics of psychiatric research in the last decade. The gut microbiota may play an important role in the development of neuropsychiatric diseases, according to a growing body of research. Gut microbiota is a key regulator of gut-brain axis and may shape our brain physiology; thus, any change in its composition may change our behaviour due to altered psychiatric conditions. Relationship of gut microbiota with different mental illnesses is discussed in this article.

Keywords: Dysbiosis. Gut-brain axis. Mental health. Psychiatric illness.

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INTRODUCTION

The human intestine accommodates heterogenous microbial ecosystem dominated by bacteria and also comprises of viruses, protozoa, archaea, and other eukaryotic microorganisms. Amazingly gut microbiota (GM) may weigh up to 1.5 kg![1] Last decade witnessed growing attention of the scientific community for the potential effect GM on human health and wellbeing. Research suggests that GM is linked to diseases including psychiatric conditions. For example, an alteration of GM may lead to metabolic syndrome, inflammatory bowel disease, colorectal cancer, obesity, allergies, type 2 diabetes, and even heart failure.[2] In addition to this, GM has been found to be associated with neuropsychiatric disorders like anxiety, depression, autism, Alzheimer's disease (AD), Parkinson's disease (PD), etc. In this article, a brief introduction to GM and effect of GM on gut-brain axis (GBA) and different mental conditions are discussed.

HUMAN MICROBIOME PROJECT

It is worthy to note that Human Microbiome Project (HMP), a ten-year long project supported by the National Institutes of Health (fiscal year 2007-2016), United States of America (USA), characterised microorganisms from healthy human participants with a mission to develop community resources of reference data sets for normal flora in human body. These resources have immense contribution in understanding the role of microorganisms in human health and diseases. The term "microbiome" means all organisms and their genetic material present in different sites of human body, e.g., skin, mouth, gut, lungs, vagina, and other exposed surfaces while the term "microbiota" represents populations of microorganisms in a body ecosystem, such as GM.

GUT MICROBIOTA

A recent comprehensive analysis showed that a healthy human gut microbiota may comprise of 157 organisms[3] and a large-scale study suggests that human gut microflora may collectively contain more than 35000 bacterial species.[4] Gut bacteria predominantly belong to three major phyla, Firmicutes, Bacteroidetes, and Actinobacteria.[5] Other than these three, Proteobacteria, Fusobacteria, and Verrucomicrobia are also present in gut environment.[6] Firmicutes phylum includes *Clostridium*, which is commonest (95%) bacterium. Other genera of this phylum include *Bacillus*, *Lactobacillus*, *Enterococcus*, and *Ruminicoccus*.[5] *Bifidobacterium* represents Actinobacteria, the less abundant phylum.[7] This general microbial composition in normal human gut usually varies within individual at different levels of gastrointestinal tract (GIT) from oesophagus to rectum. For example, *Streptococcus* is dominant in distal oesophagus while *Helicobacter pylori (H. pylori)* in stomach and *Salmonella, Vibrio cholera, Escherichia coli (E. coli)*, etc. in colon.[1,4] It also varies between individuals. Each individual possesses a unique GM profile which is determined in infancy when an individual is exposed to variety of microorganisms soon after birth through various mechanisms. These mechanisms include mode of delivery (vaginal or caesarean),

age, diet in infancy or adulthood, surrounding hygiene, use of antibiotic, stress, etc.[4,5] These microbes maintain symbiotic relationship with gut mucosa and help in the metabolism of nutrients in several ways.

Genome of this huge number of microbes considerably expands functional host genome. This expansion adds enzymes to the gut which were not encoded by the host, and used up by the host in metabolic processes.[6] GM forms small chain fatty acids (SCFA) from diet in the gut lumen. These fatty acids help in maintaining integrity of gut epithelium, glucose homeostasis, take part in lipid metabolism, regulate immune response and inflammatory events.[8] The microbes reduce formation of oxalate stones in kidney, helps in synthesis of vitamin K and components of vitamin B, synthesizes compounds with antidiabetic, hypolipidaemic, and immunomodulatory properties for both innate and adaptive immune components, helps in metabolism of xenobiotics and drugs, protects host from disease causing microbes by secreting bacteriocins, breaks down dietary polyphenols those are more easily absorbed.[4] Current research shows that GM has important role in myelination, neurogenesis, and activation as well as maintenance of microglia; thus, influences GBA, shapes our behaviour, affects mood as well as cognition.[9]

GUT-BRAIN AXIS AND MICROBIOTA

GBA is a two-way signalling mechanism between the enteric and the central nervous systems establishing communications between the intestinal activities and the brain's emotional and cognitive centres.[10] While brain stimuli affect the gut movement, secretion, and overall function, signal from gut can also affect brain function. GM facilitates this two-way communication although the exact mechanism is not fully understood. It is suggested that the bacteria may impart its impact on brain through modulating the neural network by stimulating enteric nervous system and passing the signal through vagus nerve within the spinal cord.[11] GM can even influence the hypothalamic-pituitary-adrenal (HPA) axis by inducing increased production of cytokines.[1] On the other hand, prolonged stress can affect HPA response which in turn can alter GM composition.[12] Further, stress increases cortisol level which may increase permeability of intestinal barrier (leaky gut) causing bacteria or bacterial products to invade through blood-brain barrier (BBB). This may lead to chronic systemic and neuro-inflammation. Gut bacteria can also affect brain function via host immune system. One of the major mechanisms by which gut microbes communicate with host neurones is through toll-like receptors (TLRs) of innate immune system which are abundant on the neurones.[13] GM can also generate neurotransmitters like gamma-aminobutyric acid (GABA), norepinephrine, dopamine, acetylcholine, and serotonin,[1] and can influence neural function.[11] Further, GM may also produce various neurotrophins and proteins, such as brain-derived neurotrophic factor (BDNF), synaptophysin (membrane glycoprotein found in presynaptic vesicles), and post-synaptic density protein.[14] BDNF, a growth factor, has important role in survival and growth of neurones, can also serve as neurotransmitter modulator, and influence neuronal plasticity, which is integral part of learning and memory.[15]

ROLE OF GUT MICROBIOTA IN MENTAL HEALTH DISORDERS

Mental health disorders are mostly considered as interplay between genetic profile of susceptible individuals and environmental factors. However, research outcome in recent years on gut-microbiota-brain axis adds a new paradigm in behavioural sciences and ascertains an additional direction in understanding pathophysiology of mental health disorders.

Dementia

Dementia causes memory and cognitive dysfunctions those can disturb normal activities in daily life. It is estimated that approximately 47 million people worldwide had dementia in 2015, which is expected to increase three times by 2050.[16] Recent studies suggest a relationship between GM and dementia. A change in GM can be considered as independent risk factors for developing dementia.[17] AD is the most common neurodegenerative disease and the leading cause of dementia worldwide (60-70%).[18] PD is the second most common neurodegenerative disease.

Alzheimer's disease

AD, a progressive neurodegenerative disease with declining memory and cognitive functions is marked with the presence of amyloid plaques and neurofibrillary tangles. Amyloid plaques are formed from extracellular accumulation of mis-folded amyloid beta (Aβ) proteins of amyloid precursor protein (APP) metabolic pathway, and neurofibrillary tangles are formed from hyperphosphorylated microtubular tau protein.[2] Pathophysiological aspects of AD are not fully known till date; gene mutations and interacting environmental factors are held responsible.

Recently it has been suspected that dysbiosis or loss of balance of microbiota may play an important role in the development of AD. Reduction of beneficial microbes and increase in the pathogenic forms in the gut causes these harmful species and their metabolites to invade BBB. It is found that certain viral or bacterial infection can play instrumental role in the development of AD. For example, chronic infection by *H. pylori* can induce the production of inflammatory mediators, and can also harm neurones. Other than *H. pylori*, *Borrelia burgdorferi* and *Chlamydia pneumonia* have been found to be associated with AD. A viral cause involving herpes simplex virus type 1, *Cytomegalovirus*, and varicella-zoster virus has also been suggested.[2] Dysbiosis and a reduction in species diversity may lead to decreased production of neurotransmitters by GM and altered synaptic plasticity due to reduced levels of BDNF, N-methyl-D-aspartate (NMDA) receptor, serotonin, serotonin receptor, GABA, etc. Dysbiosis may also increase production of proinflammatory cytokines leading to a state of neuroinflammation.[19] Dysbiosis can also alter the neuroprotective molecules like SCFA.[2] Studies show that dysbiosis may initiate inflammation-induced formation and deposition of cerebral amyloid-β.[20] Recent studies show that penetration of bacterial lipopolysaccharide (LPS) through BBB during chronic gut inflammation may lead to neuroinflammation with an increase in IL-6 level. Further, increased level of LPS in circulation can lead to

insulin resistance. Neuronal insulin resistance can enhance the risk of AD.[20]

Parkinson's disease

Reduced level of dopamine is a hallmark of PD which is reflected by motor impairments.[21] Growing scientific evidences show a link between GM and risk for PD. PD is often preceded by gastrointestinal disturbances emphasising possibility of an association between GM and the disorder. In a meta-analysis, Romano *et al*.[22] demonstrated that GM composition in PD patient was consistently different from that of the healthy controls. Remarkable alterations included depletion of SCFA forming bacterial species while the gut flora was found to be enriched with *Lactobacillus, Akkermansia, and Bifidobacterium* genera. Another meta-analysis suggested that an altered GM could act as an environmental trigger in the development of PD.[23] Unknown pathogen may enter GIT causing GM imbalance which eventually leads to leaky gut to reach enteric nervous system.[24] This may lead to accumulation of α-synuclein protein (Lewy bodies) causing cell death in brain's basal ganglia rich in dopamine-secreting neurones. In addition to this, pathogen can also create a pro-inflammatory environment in the gut sending signal to brain which may lead to PD progression.[24,25] However, a firm relation between GM and PD is yet to be established.

Anxiety and depression

Anxiety and depression are becoming highly prevalent worldwide. They often debilitate normal life and increase the risk to commit suicide. Pathophysiology involves modulations of neurotransmitters like serotonin, dopamine, and noradrenaline. Research suggests that disturbed GM could modulate the brain neurotransmitter which causes the physiopathology of anxiety and depression.[26]

As discussed earlier, inflammation has been held one of the major responsible causes of depression. In fact, it is found that more than 20% of inflammatory bowel disease patients develop depression.[27] A change in GM composition induces microbial LSP production, which, in turn initiates inflammatory responses, and cytokines send the signal to brain. Alternatively, gut inflammation can cause neuro-inflammation which then triggers the microglial action and kynurenine pathway[27] to develop depression.

Schizophrenia

Schizophrenia is a debilitating psychiatric disorder that may cause both physical and social morbidity.[28] Its aetiology is not fully understood, and recently GM dysbiosis is thought to be a putative cause of this disorder. *Lactobacilli* were consistently found to be elevated in different studies in the patients or in the individuals with increased risk of schizophrenia. *Lactobacilli* were also found in higher level with increased disease severity.[28] While these bacteria are known to be beneficial for health, an increased level of *Lactobacilli* in schizophrenia and as mentioned earlier, in PD, is perplexing.

Like other mental conditions, schizophrenia can also be induced by inflammation. Elevated antibodies to *Saccharomyces cerevisiae* have been reported that marks intestinal inflammation in schizophrenic patients. A dysbiosis may worsen the situation by increasing intestinal permeability and thus inflammation. Bacterial translocation marker, soluble cluster of differentiation 14 (sCD14) has been found to be increased in this disorder.[28]

Autism spectrum disorder

GM imbalances are common occurrence in children with autism spectrum disorder (ASD). Mode of delivery can have influence on development of autism. Children born in caesarean section have higher risk for ASD than those born through vagina. A history of increased number of antibiotic uses has been often reported in ASD children in comparison to the children without ASD. Antibiotics not only kill the pathogens but also can act on gut commensals, which may alter the normal GM composition.[29] Gastrointestinal problems are frequent in ASD, with higher incidences of constipation and diarrhoea in comparison to the unaffected individuals. "Leaky gut" has been found to be associated with ASD. Due to increased gut permeability, bacterial toxins get into the blood stream and affect brain function thus social behaviour score.[29] It was found that children with ASD had less diverse GM and like other mental illnesses had higher levels of *Lactobacillus*.[30] Higher level of *Clostridium histolyticum* group was also reported and *Clostridium* is known to produce neurotoxins.[31] Propionic acid, an SCFA, produced mainly by *Bacteroidetes, Clostridium*, has been suggested to be linked with ASD. Like other mental conditions, ASD has also been associated to inflammation. In ASD, *Bacteroides* those are known to have anti-inflammatory effects were found to be present in lower levels.[32]

CONCLUSION

Current research demonstrates that GM bridges GBA and is a key participant in shaping our brain and its function. Apart from helping in digestion, these microbes synthesize active molecules those are essential in brain development. Thus, an alteration of GM can induce development of mental illness. Association of GM dysbiosis has been evidenced for several mental conditions. However, these observations are based mostly on animal models (especially germ-free mice completely lacking microbiota), and few on human studies. Inflammation-mediated debilitating effects on brain seems to be the major mechanism mediating most of these illnesses. Some results from human observational studies remain perplexing and are not clearly understood so far. For example, presence of high level of *Lactobacilli*, those are conventionally known as beneficial microbes, has been recorded for more than one types of mental illnesses. Therefore, pathways relating GM and mental health should be precisely understood before conducting microbiota-based interventional studies in humans. There are few initiatives for microbiota transfer therapy, for example, re-colonisation of children's gut with ASD with bacteria from donors without ASD.[33] Scientists, however, stress that although the results of these studies seem exciting, larger trials should be conducted to reach a clear conclusion.

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