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REVIEW ARTICLE

The clinical outcomes of gut-brain axis (GBA) microbiota influence on psychiatric disorders

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ABSTRACT

The gut microbiome plays an important role in the health of the body. The study of its effect on mental problems has become the main topic of this study. As a matter of fact, every change in the gut microbiota composition can influence on mood and anxiety and vice versa. So, considering this "microbiota-gut-brain" axis (GBA) is so important. In this narrative review, the most recent reproduced information on GBA roles in neuropsychiatric disorders, and clinical significance have been considered. The gut microbial population is formed from birth and transforms from an immature state to the postnatal period into a more intricate and diverse adult ecosystem. In this review, we had some findings that GBA implicated in some psychiatric problems which can be a dysregulation consequence. In addition, some bacteria have been implicated in causing mental disorders in humans such as depression, obsessive-compulsive disorder, psychiatric disorders, stress disorders, schizophrenia and, autism. The absence of balance in GBA natural state can cause several negative consequences on host health which leads to neurological problems. Possibly, findings were delineating an interesting new etiological pathway for future exploration.

Keywords: Gut-brain axis (GBA); Microbiota; Obsessive-compulsive disorder; Psychiatric disorders; Stress-related disorders; Schizophrenia; Autism

INTRODUCTION

Microorganisms that live symbiotically in the human intestine are called intestinal microbiota.The intestinal microbiota consists of bacteria, archaea and eukaryotes. However, bacteria are the dominant population of gut microbiota. Gut microbiota has a beneficial relationship with humans (1). Approximately, 1000 different microorganisms live in the gut that regulate many physiological functions of the body. In addition to the effect of microbiota on the digestive system, these microorganisms can regulate the function of the brain and central nervous system. The "enteric nervous system" is identified as its autonomy characteristics and similarity to the central nervous system (1, 2). With studies in the early 19th and 20th century, bidirectional relationship between the brain and the gut has been recognized (1). It was reported that emotional state can change the gastrointestinal (GI) tract function (2). Brain controls and

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directs our emotions, thoughts and behaviors under different conditions. Throughout their lives, people are in situations that can lead to feelings of fear and happiness, stress, depression, and so on (3, 4). More than 100 trillion symbiotic microorganisms live on and within human beings and play an important role in human health and disease (5). The human microbiota, especially the gut microbiota, has even been considered to be an "essential organ", carrying approximately 150 times more genes than are found in the entire human genome (6, 7).

All human body microorganisms, containing eukaryotes, bacteria, and viruses explain the "human microbiota". In the other hand the complete list of these microbes and their related genes refers to "microbiome" (8, 9). Many factors such as genetics, age, diet, infection, drug use, and gender can temporarily or permanently affect the gut microflora nature. Changing this microbial composition by outer factors can cause remarkable changes in human health (10, 11). Microbiota can keep mental health. Every disruption in microbiota composition can contribute to psychiatric problems appearance. So, it has been suggested that the gut microbiota can effect and modulate the gut-brain" axis (GBA) (12). Both physical and mental sicknesses have been occurred by deregulation of host-microbiota interactions in the gut. Consequences of this dysregulation were mental sicknesses, such as depression, stress, obsessive-compulsive disorder (OCD), schizophrenia, and autism (13, 14). So, according to information mentioned above, we decided to consider the clinical outcomes of Gut-Brain Axis (GBA) microbiota influence on psychiatric disorders.

The relationship between colonization of the gastrointestinal microbiota and CNS function. The bidirectional GBA include relationship between the central and the intestinal nervous system connect spiritual and brain cognitive parts with circumferential intestinal obligation. There are different ways which these two organs are correlate together both physically and biochemically (4). Bidirectional communications inside GBA have been demonstrated by several investigations. Gut microflora relate to central nervous system (CNS) via immune, nervous, and endocrine signaling mechanisms, which are three parallel and interacting ducts. All over the circuit dysregulation can occur through every disturbance in GBA (15). Some preclinical observations have been shown alterations in GBA communication in the several psychiatric and neurologic disorders pathogenesis and pathophysiology. Primarily through involving the vegus nerve, CNS bottom-up modulation can be effected by the microbiome via neuroimmune and neuroendocrine mechanisms (16). Several microbial derived molecules including secondary bile acids (2BAs), short-chain fatty acids (SCFAs), and the metabolites of tryptophan mediated this communication (4, 15, 16). Primarily, these molecules issue signals via interaction with the mucosal immune system, enteroendocrine cells (EECs), enterochromaffin cells (ECCs). But, some intestinal barrier may cross the blood–brain barrier (BBB) by entering systemic circulation (15). These molecules over take brain sites, by vagal and spinal afferents, directly or just induce central responses via long-distance neural signaling (4). The microbiota can freely produce or contribute to the output some neuroactive molecules in addition to generating these metabolites that actuate endogenous CNS signaling mechanisms. These neuroactive molecules include γ-aminobutyric acid, 5-HT, norepinephrine and dopamine. They overtake significant receptors or accomplish adequate levels to draw out a host reaction. Actually, neurotransmitters such as acetylcholine, serotonin, dopamine, gamma-aminobutyric acid, are made in the gastro intestinal (GI) tract. At the same time and in a tuned way, brain arranges our GI tract (17). Brain takes this responsibility through secretion of hormones such as corticotrophin-releasing factor, ghrelin, oxytocin, neuropeptide Y, leptin, and a plethora of others. Therefore, both physical and mental disorders have been happened by dysregulation of this microbiome (18, 19). Fig. 1 show a schematic representation of chronic stress and depression effects on the activity of brain-gut axis.

Relation between intestinal bacteria and mental illness. There are several numbers of microbes that exist in gut and make some chemicals that affect brain functions. Lots of short-chain fatty acids (SCFAs) such as propionate, acetate, and butyrate can be produced by gut microbes through digesting fiber. SCFA affect brain and reduce appetite. Another SCFA, butyrate, create the barrier between the blood and the brain, which is called the blood-brain barrier (BBB). Gut microbes affect the brain by metabolizing amino acids and bile acids (17). Bile acids due to liver involve in absorbing dietary fats and affect the brain.

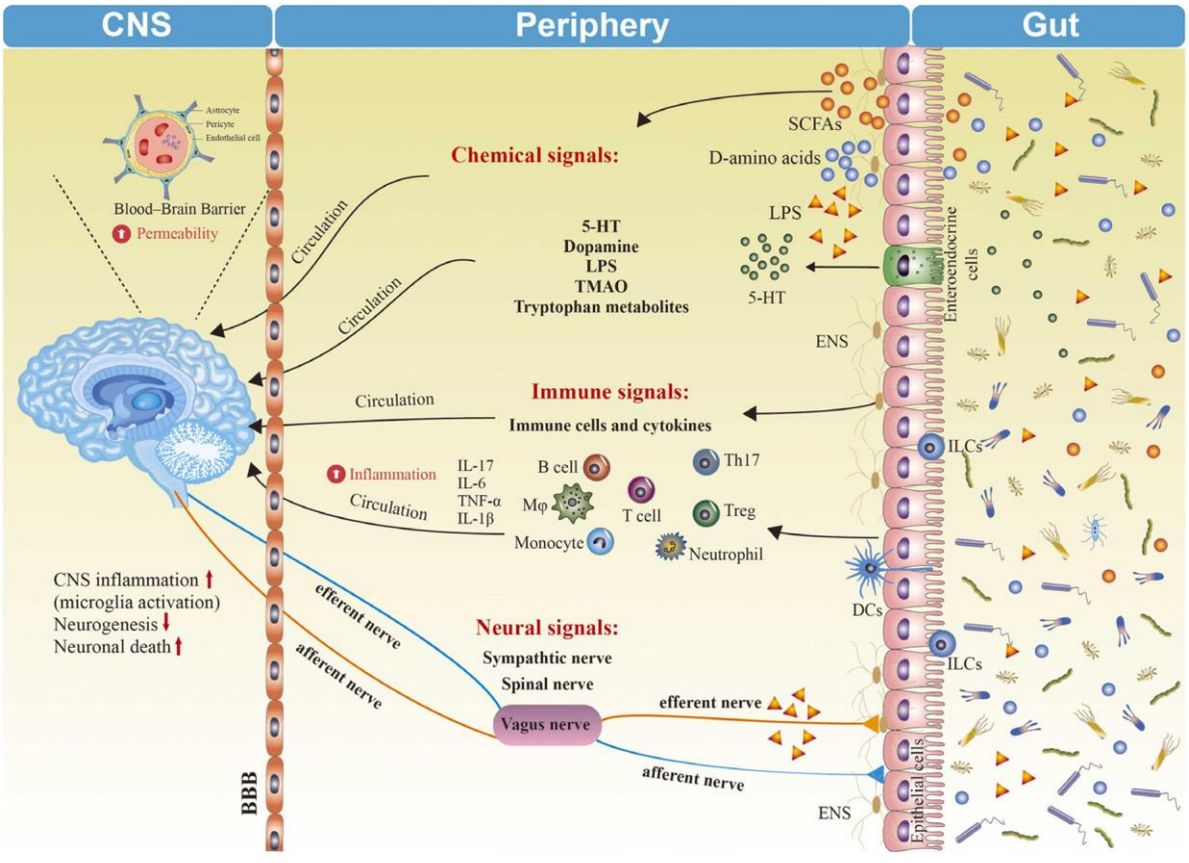

Fig. 1. A schematic representation of the effects of chronic stress and depression on brain-gut axis activity (20).

GBA have an important role in inflammation and immune response system. What is excreted and what is passed into the body can be controlled by them. In the event that the immune system is turned on for a really long time, it can prompt irritation, which is related to sadness. Lipopolysaccharide (LPS) is an inflammatory toxin, named endotoxin, which certain bacteria produce it on their cell wall. LPS can cause inflammation when pass over from the gut into the blood by becoming BBB leaky which let the bacterial LPS to enter the blood. Actually, high level of LPS in the blood has been associated with several brain problems. As mentioned, there are numerous bacteria in the gut that affect the physical and mental processes of humans. Based on research so far on gut microbiota and among the numerous microbial symbionts, *Clostridium*, *Sutterella*, *Prevotella*, *Coprococcus*, *Veillonellaceae*, *Bacteroides*, *Ruminococcus*, *Desulfovibrio*, *Lactobacillus*, *Bifidobacterium*, *Akkermansia muciniphila*, *Alkaliflexus*, *Weissella*, *Toxoplasma gondii*, *Actinobacteria*, *Xylanobacter*, *Neisseria*, *Capnocytophaga*, *Campylobacter jejuni*, *Lachnospiraceae*, *Citrobacter rodentium*, *Proteobacteria*, *Fusobacteria*, *Candida*, *Staphylococcus aureus*, *Escherichia coli*, *Fusobacterium nucleatum* are the most important bacteria that play important roles to cause the mental illnesses development such as Autism spectrum disorder (ASD), obsessive-compulsive disorder (OCD) , schizophrenia, depression (19-22).

REVIEW METHOD

Advances in the structural and functional variations understanding of gut microbiome roles in disease and host-pathogen interactions has been tended via comprehensive literature searches including the NCBI Database, Web of Science, CrossRef, Scopus, Medline, PubMed and Google Scholar were searched for study inclusion and exclusion criteria. In this narrative review, the most recent reproduced information on Gut-Brain axis role in neuropsychiatric disorders, and clinical significance have been considered.

Autism spectrum disorder (ASD). A kind of neu-

rodevelopmental disorders, named autism spectrum disorder (ASD), defined by dysfunctions in communication skills, social interaction, and behavioral observations, just as tedious practices. Many children suffer from ASD present gastrointestinal (GI) disorders (18). According to many research, some bacteria have a significant role in causing autism. Based on fecal extractive DNA research, bacteria such as *Clostridium* or *Desulfovibrio* clusters have over-represented in children with GI complaints and autism rather than to children with similar GI complaints but typical neurobehavioral. *Clostridium tetani* neurotoxin create ASD symptoms by ascending along the vague nerve route from the intestinal tract to the CNS (23, 24). In other studies the increases of *Clostridium* and *Sutterella* population with ASD were reported. A higher abundance of the *Clostridium* groups in ASD patients' fecal flora has been proven than healthy children. Mean counts of *C. bolteae* and clusters I and XI in autistic children were 46-fold (P = 0.01), 9.0-fold (P = 0.014), and 3.5-fold (P = 0.004) greater than those in control children, respectively (24). Almost, there are some bacterial species, such as *Alkaliflexus* and *Sutterella*, that have been shown to be present exclusively in autistic gut microbiota or some other bacteria as *Weissella*, were present only in healthy subjects (23). Statistics with multiple testing corrections showed significantly lower abundances of the *Prevotella* ($p< 0.001$), *Coprococcus* ($p< 0.001$), and unclassified *Veillonellaceae* ($p< 0.002$) in autistic samples. As compared to neurotypical children microbiome, the ASD subjects' microbiome was less diverse and contained lower levels of *Prevotella, Coprococcus*, and unclassified *Veillonellaceae*. It has been shown that *Bacteroides fragilis* have important role to better behavioral dysfunction in an autism mouse model. A biological marker of gut microbiota health in breast-fed infants is *Bifidobacterium* and *Lactobacillus.* Both types of microbes have important probiotic functions in the gut. They inhibit pathogenic bacteria via competitive exclusion and antimicrobial agents' production (23, 24).

Obsessive-compulsive disorder (OCD). Based on National Institute of Mental Health (NIMH) report, obsessive-compulsive disorder (OCD) is a common, and long-lasting problem which accompanies by uncontrollable, reoccurring, repeated thoughts and behaviors. There are some external environmental stress factors that have a significant role in OCD presentation. To exhibit OCD symptomology, these factors cause OCD itself or trigger an underlying predisposition. For example, stress exposure can cause lowered *Bacteroides* abundance in the cecum and raise *Clostridium* abundance. Higher fecal microbial diversity was shown in active muscular dystrophies (MD) group. *Bacteroides* and *Proteobacteria* were in individuals with active MD, and Firmicutes proportion was significantly went down. Other bacteria such as *Parabacteroides* and *Alistipes* as the primary contributors produce some neurotransmitters implicated in psychiatric disorders following as: γ -aminobutyric acid (GABA) (*Bifidobacterium, Lactobacillus*), serotonin (*Candida, Enterococcus, Streptococcus, Escherichia*), norepinephrine (*Escherichia, Saccharomyces, Bacillus*), dopamine (*Serratia, Bacillus*), and acetylcholine (*Lactobacillus*). In the lumen of intestine, these secreted neurotransmitters may enforce epithelial cells to abandon molecules for acting instantly on afferent axons or modulating neural signaling within the enteric nervous system (ENS) (25). During acute infection due to *Escherichia coli*, the Hypothalamic-Pituitary-Adrenal (HPA) axis is shown to be activated, by pro-inflammatory cytokines and corticosterone increasing. After initial *E. coli* infection, cytokine antibodies administration can attenuate the ascent in corticosterone (26). As compared to healthy, age-matched controls, some peripheral inflammatory markers producing after microglial activation in patients with main depressive episode. Additionally, ranks of studies have investigated circulating cytokines levels in patients with OCD in in correlation with control subjects. In spite of the fact that the outcomes are conflicting, many accept that this might be because of the bewildering impacts of medications and along with conditions present in study populations. An ongoing report indicated essentially more prominent plasma levels of some cytokines (such as TNF-α, IL-10, IL-6, IL-4, and IL-2) in drug-naıve, comorbidity free OCD patients when contrasted with healthy controls (27). Children with PANDA (Pediatric Autoimmune Neuropsychiatric Disorder Associated with Streptococcal infection) were found to have translocator protein receptors increasing and microglia-activated neuroinflammation. Germ-free organisms (GF mice) are multi-cellular organisms without any microorganisms living in or on them. Based on behavioral tests, microbiota reconstruction of GF mice normalize locomotors activity and anxiety behaviors during early life. At any rate, there is

a basic period in life where the anxiety response is organized. Despite the fact that the previously mentioned investigations checked the base up part of the microbiota-GBA, considers have likewise demonstrated the top-down capacity by exposing creatures to outside stressors (28).

Behavior. Human behavior is constantly changing under the influence of living environments and environmental conditions. Nutrition is one of these environmental conditions (29). Therefore, a normal behavior ensures proper nerve base, the first task of proper nutrition is to provide health and function. Dietary changes, antibiotics, and probiotics manipulate microbiome (26, 27). According to researches, changes in the microbiota affect human behavior. Studies have shown that every defect in GI barrier or alterations in microbiota of MIA (maternal immune activation) mouse model can display ASD features (28). It was demonstrated that *B. fragilis* modulated several metabolites levels. Mice treating with a metabolite, which is restored by *B. fragilis*, causes certain behavioral irregularities, and showed that the bacterial effects of gut on the impact behavior of host metabolome (26). Experiments on the GBA connection identified beneficial effects with the administration of probiotic strains in rodents or humans with neurodevelopmental disorders. In terms of 'psychobiotic' effects, major strain and species differences were occurred. Some microbes such as bifidobacteria and lactobacilli had positive effects on autism-related behaviors, anxiety, cognition, and depression. *L. rhamnosus* (JB-1) had a direct effect to physiological and behavioral responses with depending on the vagus nerve (27). Alongside these results during treated rats with the probiotic *Bifidobacerium* infantis, and an increase in tryptophan levels was reported. This probiotic had antidepressant action in depression preclinical models with a mental health *benefit* (24). Rival with live *Campylobacter jejuni* activates brain regions related to autonomic function via a vagal pathway. *C. jejuni* increases anxious-like behavior and anxiety level by the number of c-fos expressing cells in the bed nucleus of the stria terminalis (BNST), a main component of the extended amygdala fear system (29). *Citrobacter rodentium* used to investigate gut-brain axis function. When *C. rodentium* tested 14 and 30 days after infection in C57BL/6 mice, it did not affect baseline behavior (30, 31). But, in other research when Carworth Farm -1 (CF-1) mice were tested at 7-8 h following infection; an increase in anxious-like behavior was seen. More than 90% of serotonin is made in gut, which is the key neurotransmitter responsible for regulating mood. Antidepressants block the brain's serotonin receptors. Based on research conducted, when the *Candida* population increases, it creates a layer over the intestines, suppressing the serotonin production. *Candida* release toxic by products into body by breaking down the barrier of the intestine and penetrates the bloodstream (29).

Stress. Stress is the body's reaction to any change and psychologists believe that stress is a condition or feeling in which the person perceives that sum of his or her expectations is beyond his or her resources, and abilities. Apart from this definition and psychological proof, there are other testimonies (31). One of these reasons is the presence of some bacteria. Based on research conducted in this area, maternal infection, acute stress, and hydrogen peroxide can opposite the permeation induced by some probiotics such as *Bacteroides fragilis, Lactobacillus farciminis,* and *Lactobacillus salivarius* (32). In some studies oral administration of some bacteria such as *Citrobacter rodentium* and *Campylobacter jejuni* (food-borne pathogens), can activate stress circuits via vagal path activation (17). During the acute infection due to *C. jejuni*, cFOS induction (the neuronal activation marker) was evident in vagal sensory neurons in a systemic immune response absence (18). Also, during some periodontal infection, *Fusobacterium nucleatum* enter to circulation by translocating from the oral cavity and where they eventually overtake and invade the pregnant women (33). It is important to demonstrate the possibility of oral microbes' roles related to stress response to PTB (pre-term birth). Anyway it was known that stress exposure can rearrange gut microbiota composition, and microbes were capable to translocate from intestines lumen to body interior (22).

Depression. Major depressive disorder or in short depression, is a common and serious medical illness and like other mental disorders, is accompanied by symptoms that alter the normal course of daily life. As with other psychiatric disorders, based on research, bacteria in gut have a key role in causing it. It was proven that *Lactobacillus acidophilus* can play important role for depression. It is a microaerophilic bacterium and colonized the human and animal gastrointestinal tract and mouth. CB1 or CB2 receptors

prevent post-stroke depression stimulation. Generally, CB1 receptors are located throughout the body and especially in the brain. Mostly, CB2 receptors are found in the gastrointestinal tract and immune system. In one study when rats given *Lactobacillus acidophilus*, cannabinoid receptors expression in the brain stem were increased. Actually, the stimulation of CB1 or CB2 receptor prevents post-stroke depression (30). A commonly used probiotic organism is *Bifidobacterium infantis* which is a predominant bacterium in infant gut. Several studies demonstrated decreased level of tryptophan in patients with depression (32). In one of the studies when rats were fed with *Bifidobacterium infantis* orally, increased plasma tryptophan level was monitored (33). Further exploration of the link between microbiota combination and depression; have been observed with being low population of *Bacteroidetes phylum* in depressed patients. Also, a *Lachnospiraceae* family association with the depression group was reported (28, 31). Actually, bacterial translocation and being gut permeability cause to increase inflammation in depressed individuals (33). Recently, evidence supported this suggestion by observing an increasing in IgM and IgA serum levels against the lipopolysaccharide (LPS) of gut commensals in patients with depression (34). Another bacterium called *Oscillibacter*, has valeric acid which is a homolog of GABA as bacterial main metabolic and end product. GABAergic deficit is a major depression common denominator which points to a potential GABAergic therapeutic approach in major depressive disorder (32). *Citrobacter rodentium* and *Campylobacter jejuni*, which are food-borne pathogens oral administration, provide evidence that GI tract normal flora can activate stress circuits via vagal pathways activation (31, 32).

As mentioned in the previous sections, this effect is also age dependent; because the microbiome is a dynamic entity. It was influenced by some factors as metabolism, diet, genetics, age, antibiotic treatment, geography, and stress. GF mice standardized with SPF feces at birth or at age- 3 weeks modified normal anxiety-like behavior. GF mice conventionalized at age- 10 weeks showed decreased anxiety-like behavior similar to that of adult GF mice (34). Based on the findings and studies on childhood and adolescence, microbiota structure and function were the most dynamic. Therefore, it is necessary to study how GBA influence on brain health, and develop mental illness risk (35).

Schizophrenia. Schizophrenia which is a chronic and severe mental disorder is not as common as other mental disorders. The symptoms can be very disabling and like other mental illnesses relate to gut. *Lactobacillus* and *Bifidobacterium* are among the bacteria that have been implicated in stress studies. GABA producers, *Bifidobacterium* and *Lactobacillus*, were deemed effective in metabolizing gluten (10, 36). Probiotics or anti-inflammatory species, can suppress this immune reaction. Reports have demonstrated that beneficial microbes administration can decrease both inflammation and anxiety or distress behavioral signs (39). A characteristic dysbiosis signature was proven in other studies on schizophrenia patients by increasing in *Eubacterium*, lactic acid bacteria, *Candida* population and a marked reduction of *Haemophilus*, *Neisseria* and *Capnocytophaga* (37). Serologic responses to *Toxoplasma gondii*, belongs to the apicomplexa family, were increased in schizophrenia. This coccidian can cause immunopathology in small intestinal and induce colitis and ileitis, experimentally. The presence of antibodies to *Toxoplasma gondii* in individuals with schizophrenia was correlated with antibodies directed against food antigens. This reinforced the theory that an immune response to specific antigens was a higher priority than the presentation alone. Immune sensitivity increasing to gluten and bovine casein has been found in schizophrenia patients across multiple studies (38). According to research, *Actinobacteria* is one of the bacteria that causes depression and were deemed effective in metabolizing gluten. For more depression may also be age dependent. Children of mothers with pre-birth gonococcal diseases were high risk to extend schizophrenic psychosis in later life (20-22).

Controversial associations between gut-brain axis roles in neuropsychiatric disorders. A number of clinical observations report increased gut permeability and/or permeability-related parameters in patients with schizophrenia, ASD, depression, or Parkinson's disease (PD) (28). In the case of schizophrenia and ASD, most of the evidence supporting an association with alterations of gut barrier comes from studies that have design problems. In addition, there are conflicting findings showing no changes in intestinal permeability for schizophrenia and ASD when compared to healthy volunteers, and these studies have in general a better experimental design (24).

Regarding depression and PD, there are very few

studies and although they all show that patients display increased gut permeability or permeability-related markers, more and larger studies are necessary to confirm these observations (28). The use of gluten-free casein-free diets to improve intestinal barrier function and in turn treat disorders such as autism and schizophrenia has also produced conflicting results and is therefore not yet recommended as formal treatment by the expert medical community (13, 14).

With regard to pre-clinical data, it has been shown that animal models designed to replicate symptoms of autism or stress display gut barrier disturbances. In these adequately controlled, well-validated animal models, restoration of the CNS function occurs along with improvement of intestinal barrier function (31).

Future research efforts in the clinical field should focus on randomized, controlled trials as well as prospective studies when possible. For both clinical and animal studies, the contribution of intestinal microbiota to the development and treatment of CNS disorders appears as a promising field of research (37). Evidence of altered intestinal permeability in individuals suffering from CNS disorders is limited and cannot be regarded as proven. Moreover the efficacy of targeting gut barrier in the management of neurological and behavioral aspects of CNS disorders has not yet been established, and needs further investigation (38).

Fig. 2. show potential pathways connecting the intestinal lumen and the CNS. There are some important relation between brain and gut. Probiotics with the capacity to positively impact on symptoms of depression or anxiety have recently been termed psychobiotics (40). There are to date no published studies of the use of probiotics in major depression whereas they are effective in IBS.

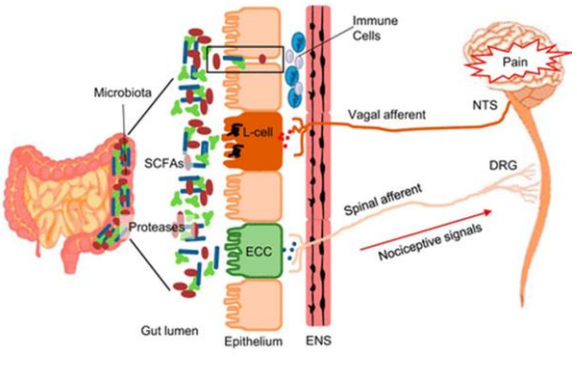

Fig. 2. Potential pathways connecting the intestinal lumen and the CNS (39).

Modulating the microbiota using antibiotics has been the subject of some investigation. Some studies have demonstrated the efficacy and sustained improvement of IBS symptoms with rifaximin treatment, while studies in depressed patients indicate the efficacy of minocycline which impacts on both Gram negative and Gram positive bacteria. Data indicate that patients with psychotic depression respond to a combination of an antidepressant and minocycline in combination (41-44). Interestingly minocycline has also been shown to reveres some of the motor and cognitive effects induced by olfactory bulbectomy (45). This increases the possibility of the behavioral changes in this model probably be due to alterations in microbial composition in the gut. To date there are no reported studies of antibiotic therapy focusing on psychiatric co-morbidities in IBS (20, 42). However, it is intriguing that both IBS symptoms and those of depression respond independently to antibiotics, providing important evidence for the role the microbiota plays in regulating brain function (43).

In summary, using a variety of techniques our understanding of the ways in which the microbiota influences the brain and behavior is gradually unraveling. This will allow for a more complete understanding of the brain-gut axis miscommunication in chronic stress states such as depression and those thought underlying the common co-morbid affective disturbances associated with IBS. What we require at this point are appropriately phenotyped patients and a judicious use of the various techniques including functional imaging and in depth pyrosequencing of the microbiome (20).

CONCLUSION

As the above mentioned the gut microbial population is formed from birth and transforms from an immature state to the postnatal period into a more intricate and diverse adult ecosystem. Absence of balance in its natural state can have negative consequences on host health and cause several problems in immunological, gastrointestinal, and neurological state. In the past decade, many studies have been done on the relationship between mental disorders and changes in the intestinal microbial composition, and all these studies have shown that intestinal microbial flora composition has a considerable role in human mental health.

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