Depression and the Microbiome

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Abstract

An intriguing topic that has captured the interest of many scientists is the brain-gut interaction. A growing body of literature elucidates that the microbiome residing within the gastrointestinal tract interacts with the brain and affects mental health. This is possible through the microbiome's ability to modify behavioral and cognitive brain activities through the synthesis of neuroactive molecules, vitamins, and Short Chain Fatty Acids. The microbiome dates back to early stages of life yet as we grow it continues to be affected by genetic and environmental factors. It is shown that disturbances in the microbiome homeostasis decode into different illnesses ranging from metabolic conditions to neurologic and psychiatric diseases. In depression, certain intestinal bacterial strains are found to be either depleted or augmented. The bacterial phyla correlated with depression will be reviewed in this paper, in addition to recent therapeutic implications that alleviate depression symptoms and adjust the microbiome.

Keywords: Depression, Microbiome, Microbiota, Diet, Probiotics, Prebiotics, Fecal Microbiota Transplant

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Introduction

Depression is a major cause of global burden leading to health complications and in some cases, to suicide. Over 300 million people in the world suffer from depression, making 4.4% of the world's total population [1]. People with depression exhibit altered brain regions and circuits that are implicated in the pathophysiology of the disease. In individuals diagnosed with major depressive disorder (MDD), neuroimaging techniques spotted decreased volumes of the prefrontal cortex, anterior cingulate cortex, thalamus, basal ganglia, and hippocampus [2]. Numerous studies have reported abnormalities in corticolimbic connections in depressed subjects, one of which denoted a decline in anterior cingulate connectivity with the thalamus, amygdala and striatum[3]. For decades many factors were believed to contribute to depression and the main factor was chemical imbalance. However, depression is a much more complex disorder. In fact, living microscopic agents are proposed to intervene with the human mental state and behavior. These agents are: Gut Microbes.

The gastro-intestinal (GI) tract is a neural, endocrine, immune organ that harbors microbes interacting with the brain through the gut-brain axis [4]. This interaction is bidirectional and ensures proper functioning and well-being of the body via various underpinning networks, exemplified by the enteric nervous system (ENS). The vagus nerve serves a crucial role in allowing the central nervous system (CNS) to communicate with the ENS. The vagus nerve informs the CNS with what is happening in the gut in order for the CNS to decipher and generate a suitable response for information received [5]. Surprisingly, the gut microbiota contains an about 150 times more genes than the whole human genome [6]. The first study documenting the ability of gut bacteria to impact behavior was demonstrated in a series of studies using Campylobacter jejuni pathogen in mice [7]. Since then, remarkable new studies have bolstered the pivotal relationship existing between the mental health status and gut microbes; one of which revealed that modern antidepressants can regulate the microbial profile and consequently reduce depressive-like behavior [8].

Why are Gut Microbes Essential?

Microbes in the body maintain a dynamic gut-brain interaction through synthesizing neuroactive molecules such as histamine, serotonin, and dopamine which all affect the host neurophysiology [9].The microbiota catabolizes tryptophan, a serotonin precursor, to several compounds such as indole, indole-3-acetate, and tryptamine [10]. In mammalian hosts, these metabolites activate the aryl-hydrocarbon receptor which is expressed in the CNS and has a key role in hippocampal neurogenesis and contextual fear memory [11]. One study showed that this activity is absent in germ-free mice which resulted in elevated hippocampal serotonin levels as well as high concentrations of tryptophan in the plasma [12].

Moreover, gastro-intestinal bacteria can synthesize and supply a family of vitamins such as riboflavin (B2), folate (B9), and cobalamin (B12). B vitamins play a crucial role in the body and brain, thus deficiencies in these vitamins manifest in a variety of psychiatric and neurological symptoms [13]. A research finding showed that one third of depressed patients exhibit vitamin B9 deficiency which implicates that folic acid could be involved in depression pathology [14].

Furthermore, gut bacteria can secrete bioactive chemicals such as choline and bile acid. Choline is an essential nutrient metabolized by the microbiota and participates in the synthesis of myelin sheath surrounding axons [15]. In adult mice and their offspring, reduced choline availability led to an increase in depressive and anxiety-like behavior [16]. Urinary choline concentrations are found to be lower in moderate MDD patients and higher in severe MDD when compared to controls [17].

As for bile acids, they can activate several receptors expressed throughout the CNS and modulate inflammatory responses [18]. Bile acids may contribute to MDD by disrupting tight junctions and making central and intestinal epithelial cells permeable [19].

Bacteria can also produce short chain fatty acid (SCFA) metabolites such as butyrate, propionate, acetate, and valerate which can all pass through the blood brain barrier to be involved in neurotransmitters synthesis [20]. SCFA are used as nutrients for brain microglial cells to support their maturation and proper functioning [21]. Acetate, propionate and butyrate are found to be depleted in MDD patients [22-23]. A recent study showed that SCFA administration to mice alleviated depression symptoms [24].

Disturbances in the axis or dysbiosis of the gut microbiome can occur due to environmental risk factors such as stress, westernized diet, and antibiotics [25-26]. As a result, tight junctions which connect cells lining the gut, loosen up and thus allow bacteria and proteins to penetrate from the gut and into the bloodstream[27]. Consequently, the gut-brain biochemical signaling is disrupted and contributes to intestinal inflammation triggered by the release of lipopolysaccharides into blood, alterations in microbial repertoire, and improper emotional responses [28-29]. Hence, perturbation of the complex network linking the microflora to host cells is decoded as neuropsychiatric disorders like anxiety, depression and other disorders[30].

Microbial Profile in Depression

Extensive research on both mice and humans enabled researchers to understand how certain microbial compositions are associated with clinically diagnosed depression. In a recent systematic review, 50 taxa were significantly ($p<0.05$) different between MDD and healthy controls [31]. A study collected fecal samples from MDD patients and healthy controls to measure the microbial gut content. It showed that there was a noticeable increase in Actinobacteria, Bacteroidetes, and Proteobacteria phyla while a decrease in Firmicutes phylum in the MDD group compared to the healthy one [32-33].

Moreover, an experimental study showed Lactobacillus to be reduced in piglets after the exposure to stress [34], so this suggests a possible direction of causality from the brain to the gut. In addition, a recent study analyzing fecal microbiomes of participants from the Belgium Flemish Gut Flora and Dutch LifeLines DEEP Projects revealed that both Coprococcus and Dialister bacteria are depleted in depressed individuals even after adjusting for antidepressant usage. Interestingly, the study discovered that Bacteroides enterotype 2 associated with Crohn's disease, were also prevalent in patients suffering from depression [35]. Of course, association in these studies does not necessarily mean causality as it could be that depressed people have different lifestyles and eating habits and this could consequently alter their microbiota composition. Nevertheless, these results are of the strongest yet to display that a person's mental health is influenced by his gut and vice versa.

Treatments and Preventive Strategies

Most pharmacological medications that target neurotransmitters activity in the brain demonstrate a delayed onset of effect as well as a range of side-effects. Adding to that 30-40% of MDD patients do not respond to antidepressant drugs [36]. Therefore, finding alternative approaches to treat depression is of key importance.

a) Diet

A balanced diet serves as a cost-effective, nonpharmacological intervention that reduces the risk of developing many diseases. The brain relies on a continuous nutritive energy supply acquired from food in order to function properly. Eating habits modulate the gut microbiota and inflammation which are both known to be involved in the pathogenesis of psychiatric disorders [37]. According to numerous studies, the plant-based Mediterranean diet (MD) is recognized as a mental health booster. It is rich in vegetables, fruits, whole grains, nuts, beans, unsaturated fats and it is low in animal products. The most preferred animal protein supply is fish due to its richness in omega-3 fatty acid that decreases triglycerides and reduces the risk of cardiovascular diseases [38]. Researchers examined the effect of MD supplemented with fish oil in people with severe depression and discovered that the MD reduced depression symptoms [39]. MD also ameliorated gut microbe diversity and diminished chronic inflammation that accompanies depression [40].

Another dietary approach that is highly recommended for its high-fat, low-carb properties is the ketogenic diet (KD) [41]. It forces the body to use fats or ketone bodies as energy sources instead of using carbohydrates or glucose. KD has been considered for a variety of neurological conditions such as epilepsy, multiple sclerosis and Alzheimer's disease [42-44]. It is widely adopted as a treatment for children with refractory epilepsy due to its efficacy in reducing seizures as well as pathogenic Proteobacteria [45-47]. KD is also studied in psychiatric disorders like autism spectrum disorder, schizophrenia, bipolar disorder, attention deficit hyperactivity disorder, and depression. However findings are mostly limited to animal models[41]. In rats, KD increased physical activity and boosted some brain areas and this result was similar to that produced by antidepressants [48-49]. To the best of our knowledge, there are no published studies investigating KD effect on the microbiome of depressed patients. Studies reporting KD effects on microbiome composition provide preliminary data, indicating that it is a powerful tool worthy of further clinical trials.

b) Probiotics

Variability in the abundance of specific bacterial strains paved the way for novel approaches to treat clinically diagnosed depression. Probiotics are oral bacterial supplements targeting the microbiome. They play a major role in maintaining gut ecosystem equilibrium by regulating neurotransmitters and significantly reducing depression in populations aged under 60 [50]. Not only that but probiotic consumption also decrease pro-inflammatory cytokine levels like tumor necrosis factor-alpha, interleukin-6 and IL1β and thereby significantly reducing inflammation [51].

According to Marin et al, yogurt might have a therapeutic role in depression. The study showed that depressive-like behavior in stressed mice were improved after being fed Lactobacillus reuteri. The latter is a probiotic present in yogurt and is responsible for controlling kynurenine metabolite level in blood which is linked to depression [52]. Another animal study observed the impact of Lactobacillus plantarum in germ-free

mice and reported an antidepressant effect and augmented levels of dopamine and serotonin in the striatum. On the other hand, Seguimiento Universidad de Navarra Project demonstrated that whole-fat yogurt intake was associated with reduced depression risk while low-fat yogurt consumption was associated with a higher risk [53].

Several clinical trials that focus on probiotic consumption to relieve depressive symptoms have been and are still being conducted. A positive effect on the mood of healthy female volunteers was reported after a four-week administration of a probiotic mix containing 9 bacterial strains [54]. Following thirty days combinatory treatment of Lactobacillus helveticus and Bifidobacterium longum in healthy adults, cortisol levels were lowered and so were depression and anxiety levels [55]. A randomized, double-blind, placebo-controlled clinical trial was carried on MDD patients aged 20-55 years old and they received capsules containing 3 strains for 8 weeks. The strains were Lactobacillus casei, Lactobacillus acidophilus, and Bifidobacterium bifidum. Throughout the study, participants were ordered to abide to their usual diet and activity and stay away from medications that might impact the intervention. At the end of the intervention, there were significant improvements in insulin function and the score of Beck Depression Inventory in comparison to the placebo group [56]. Additionally, in New Zealand, 193 mothers in the postpartum period received Lactobacilus rhamnosus HN001. A significant decline in post-natal anxiety and depression scores was reported and this suggested that HN001 might serve as a potent treatment for reducing depressive symptoms after delivery [57].

A meta-analysis by Ng et al, which included 10 randomized clinical trials investigating efficacy of probiotics, found no significant effect of probiotics on mood as compared to placebo[54]. However, a more recent meta-analysis included 19 double-blind, randomized, placebo-controlled trials, 8 of which were included in Ng et al meta-analysis, found that compared to placebo, probiotics were associated with significant improvements in depressive symptoms. Upon stratifying the analysis into three groups, probiotics were significantly superior to placebo in alleviating depressive symptoms among MDD patients, but not among other medical conditions or the general population. Upon further stratification, the probiotics were effective in reducing depressive symptoms among MDD patient whether they were receiving or not receiving an antidepressant. In addition, the analysis suggested that multiple strains probiotics might be more beneficial in reducing depressive symptoms than single ones [58,59].

Currently, othertrialscovering Lactobacillusand Bifidobacterium supplementation to people diagnosed with depression are being processed [60-61]. A probiotic supplement containing 8 strains of live bacteria, has been tested in MDD participants taking antidepressants to see if it boosts the medication's effect [62]. The underlying mechanisms and effects of probiotics on depression are still not fully understood, but what's known is that their consumption ameliorates carbohydrate malabsorption [63], increases plasma tryptophan level and decreases serotonin and dopamine concentrations in the frontal and amygdaloid cortices respectively [64]. Despite the focus in most studies on positive role, further studies reporting adverse effects should be considered [65].

c) Prebiotics

Unlike probiotics, prebiotics are indigestible fiber compounds that ferment in the GI tract where they are consumed by the gut bacteria. Fermentation of prebiotics by the gut flora produces SCFAs, including butyric acid, lactic acid and propionic acid. These products diffuse to blood circulation and affect different organs.

The most commonly-studied prebiotics that promote the growth of good bacteria are Galacto-oligosaccharides (GOS), Fructo-oligosaccharides (FOS), and resistant starch (RS) [66-68]. GOS are plant sugars naturally found in beans, dairy products, and certain root vegetables. Fructans or FOS, on the other hand, are natural sweeteners that control which bacteria ferments them based on fructose chain length [69]. Both GOS and FOS regulate brain-derived neurotrophic factors, synaptic proteins, and neurotransmitters [70]. In healthy volunteers, cortisol awakening responses were significantly reduced after three weeks supplementation of a commercial prebiotic Bimuno®-GOS. However, the supplementation of FOS showed no effect [71]. Mice exposed to psychosocial stress were given a combination treatment of FOS/GOS that lowered their pro-inflammatory cytokines and demonstrated an antidepressant effect [72]. Both FOS and GOS are shown to augment Bifidobacteria as well as diminish inflammation by enhancing intestinal barrier integrity and inducing anti-inflammatory signals [73-74]. Resistant starch like oats, green bananas, and potato starch function as soluble fibers in boosting the number of beneficial bacteria. In an animal model, the gut microbiome was quantifiably altered after the administration of RS [75]. In addition, an RS dietary crossover study provided key insights by showing how high-RS diet augmented the ratio of Firmicutes to Bacteroidetes and activated several enzymatic pathways [76]. Unfortunately, this type of treatment remains under-investigated regarding its impact on the central nervous system and mood disorders.

d) Fecal Microbiota Transplant

It is believed that FMT might serve as a viable treatment by helping adjust bacterial gut profile and clearing infection in ailing patients. FMT is defined as the transfer of gut microbes from a healthy donor feces to a recipient. Potential donors undergo laborious screening of history, blood serum, and feces to minimize the risk of infection or disease transmission. There are various ways to perform FMT, one of which involves the use of colonoscopy to insert liquefied and filtered stool into the colon. Other methods include capsule ingestion, flexible sigmoidoscopy or enema, and nasoenteric or feeding tube. So far, this therapy has been shown to be effective in treating Clostridium difficile infection, autoimmune diseases, and inflammatory bowel disease [77,78]. Interestingly, remodeling gut microbiota through FMT not only recovers digestive functions, but also improves neuropsychiatric disorders [79].

Currently, there are no published human intervention studies investigating the transfer of healthy fecal flora to MDD individuals, but a few are ongoing. Nevertheless, more research is required to determine the proper functioning of FMT technique on humans because animal models do not accurately mirror human behavior. A recent unfortunate incident involved the death of an immunocompromised patient who underwent FMT. This led to FDA issuing a safety warning over fecal

transplants that might be associated with the transmission of extended spectrum Beta-lactamase E. coli from the donor's stool [80,81]. Standardized protocols for donor screening, stool preparation, and delivery mode should be followed cautiously in order to maintain patient safety and survival.

Conclusion

The role of microbiota in balancing the brain and body has rapidly emerged, but further investigation is warranted to reach causality between depression and intestinal flora. The network connecting the microbiome and brain is enormously dynamic and complex to an extent that any change at the molecular level results in defects in both. A lot of research has been invested in the management of mental illness, yet major issues haven't been resolved yet like lagging human data, small sample sizes, and confounding factors (drugs and dietary intake). It is also important to highlight that the vast majority of research to date has been conducted on animal models and more human research is needed. Therefore, resolving a chronic mental condition such as depression requires the implementation of larger randomized clinical studies along with follow-ups in order to design individualized regimens and novel microbe-based formulations. Indeed, the microbiome health is a fundamental domain of study that should be given more attention in the future.

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