The Importance of Gut Microbiome in the Modulation of Depression

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Depression is the second leading cause of disease burden worldwide and ranks highest in psychiatric disorders prevalence (Ferrari et al., 2013). While mental health has been put in the forefront of research, there is still uncertainty about the neurophysiological causes of depression. With growing research on the bidirectional relationship between the gut and the brain, scientists have begun to explore how gut microbiome diversity relates to depression. Previous studies have demonstrated that there is a significant association, and further blocking and mimicry studies point to a direct link between the gut microbiome and depression. This paper will present evidence that establishes the gut microbiome as necessary for the modulation of depression.

The Gut-Brain Axis Overview

In utero exposure to compounds that mimic estroThe brain has long been understood as the body's command center, regulating body functions and maintaining homeostasis through the central, peripheral, and enteric systems. As a complex organ that perceives, integrates, stores, and communicates internal and external information, the brain interacts with all the physiological systems throughout the body. The gastrointestinal (GI) tract, also known as the gut, is primarily responsible for the digestion of food, absorption of nutrients, and excretion of waste. These functions are critical to sustaining life and maintaining homeostasis for organisms. Furthermore, the gut has its own microbiome, host to a diverse and complex environment of microorganisms, including bacteria, archaea, and eukarya living in symbiosis with the human body. Probiotics are beneficial bacteria that live in the gut or can be ingested, and they aid with general digestive system functioning and are also critical in immune functioning (Thursby & Juge, 2017). The existence of many microorganisms' families and types is crucial for maintaining homeostatic functioning, and when diversity is lost, gastrointestinal capabilities generally decline.

In recent years, more attention has come to how the cognitive and emotional functions of the brain interact with gastrointestinal functions through a bidirectional relationship. A common communication pathway in the gut-brain axis is the hypothalamic pituitary adrenal (HPA) axis, a branch of the autonomic nervous system. This pathway is exemplified by how psychological stressors can alter gut functionality. The ANS sends signals that lead to the alteration of motility, intestinal permeability, immune function, and more (Chen, Xu, & Chen, 2021). Inversely, the gut microbiota also has modulating effects on brain functioning. While the CNS communicates with various parts of the body, what sets the gut apart is its complex neuron network which is made of 200 to 600 million neurons (Mayer, 2011). Since these neurons are located in the gut, gut microorganisms can interact with them. The microbiota can thus have an upstream influence on the CNS through metabolic and neuroendocrine pathways (Carabotti et al., 2015).

Depression Overview

Depression can be characterized in various dimensions, from neurobiological to psychobehavioral. In clinical settings, depression is determined based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria. Some criteria include depressed mood, diminished interest or pleasure in activities, significant weight loss, slowing thought processing or physical movement, and fatigue (APA, 2022). Depression is an etiologically complex disorder that can be investigated from various lenses. The monoamine hypothesis suggests that depression results from low levels of neurotransmitters like serotonin and norepinephrine (Rot, Mathew, & Charney, 2009). Monoaminergic antidepressants are commonly used to treat depression, but the response rate is low (Martín-Hernández et al., 2021). Furthermore, some researchers point to stress as a precipitating factor for depression.

They posit that stress interacts with genetic factors of individuals that influence their risk for depression. It is just as imperative to consider the gut-brain axis when investigating depression etiology because research seems to support already existing pathways between the gut-brain axis and hypothesized depression mechanism. Exploring a more causal relationship between the gut and depression may provide new insight in how we approach depression diagnosis and treatment.

Finding the Connection

Extensive research has investigated the connection between the gut microbiome and depression. For example, patients with depression were found to have lower counts of *Bifidobacterium* and *Lactobacillus* than people without depression (Aizawa et al., 2016). Previous studies have determined that *Bifidobacterium* and *Lactobacillus* are probiotics that promote stress response and psychological well-being, so the study focused on these bacteria. They found this association by taking fecal samples from patients with depression and healthy controls. The bacteria were counted through a bacterial rRNA-targeted reverse transcription-quantitative polymerase chain reaction. This study sets the foundation for exploring which bacteria are essential for modulating depression.

Furthermore, a systematic review found that across multiple studies, researchers have found that there is a correlation between depression and altered composition of gut microbiota in depression. Their quantitative synthesis consisted of nine studies that control for comorbidity and experiment procedure. Like the previously mentioned study, this review found certain bacteria at low abundance in people with depression. However, they also found that there are classes of bacteria that have a high abundance in people with depression, suggesting these bacteria could be influencing depression. Although they found trends that point to gut microbiome alteration in people with depression, the results did not indicate consistent patterns in terms of microbiome diversity. Therefore, conclusions cannot be drawn about specific microbiota that impacts depression but rather supports the idea that gut alteration is associated with depression.

A major limitation of association studies is that they often do not control for confounding variables that could impact the expression of depression or gut microbiota diversity. This limits the conclusions that can be drawn about the relationship between the two variables. With this in mind, researchers have been utilizing experimental methods that specifically investigate the relationship between the gut microbiome and depression.

The Depletion of Gut Microbiome and Depression

A common experiment model used in exploring the relationship between the gut microbiome and depression is using animal models that have their gut microbiome altered. A study found that when antibiotics that compromised the gut microbiome were administered to mice, they showed depression-like behavior (Guida et al., 2018). They administered an antibiotic cocktail of Ampicillin, Streptomycin, and Clindamycin in water to healthy mice for two weeks. The exposure to antibiotics led to an imbalance of gut microflora, which is known as dysbiosis. The control mice were given sterile water. The depression behavior of increased immobility time in the tail suspension and forced swim test were observed in dysbiosis mice compared to the healthy mice. Unlike simple association studies, this experiment manipulated the gut microbiome to observe the implications it has on depression-like behavior.

To further emphasize their point, the researchers treated the dysbiosis mice with probiotics with the intention of restoring some microbiota diversity. Repeated probiotic treatment for the dysbiosis mice resulted in a decrease in immobility in both experimental conditions. This study further underscores the direct effect of gut microbiota on depression expression.

Although this is a promising study in terms of validating those changes in the gut microbiome influences depressive behavior, it is important to note that it does not confirm what part of gut microbiome influences depressive behavior. For example, another study found that germ-free mice should show a decrease in depressive-like behavior (Zheng et al., 2016). In this study, researchers used germ-free mice rather than treating the mice with antibiotics. Germ-free (GF) mice, which are considered sterile and lack microbiota, were used as the experimental group (Qv et al., 2020). They were compared to specific pathogen free (SPF) mice that contained microbiota but were free of pathogens that might confound the data. In this study, the alteration of the gut microbiome led to a decrease in depression-like behaviors. Thus, no conclusions can be made about if its certain bacteria induce depression or if there are bacteria that prevent depression. Nevertheless, both studies

weaken the argument that the relationship observed in the association studies are due to confounding variables. Rather, these studies emphasize that there is a direct connection between the gut microbiome and depression.

Fecal Microbiota Transplantation

One method of investigating the impact that changes in the microbiota have on organisms is fecal transplants. This protocol typically takes fecal samples that contain a certain microbiota diversity and transplants them into an organism that is either lacking or is different from the donor (Kelly et al., 2015). The transplanted microbiota becomes integrated into the recipient's system and can result in biological and behavioral changes. Fecal transplants have been used to further the understanding of the relationship between microbiota changes and neurobehavioral outcomes.

One study found that when fecal samples from patients with MDD were transplanted to microbiota-depleted rats, the recipient animals exhibited physiological and behavioral characteristics of depression (Kelly et al., 2016). Patients were recruited from psychiatric clinics and had been diagnosed with MDD based on The Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria. Furthermore, people were excluded from the study if they had anything that could confound the data. For example, exclusion criteria included if they used probiotics, had taken antibiotics recently or had a history of bowel disease. The adult rats were given an antibiotic cocktail to cause dysbiosis for 28 days before the fecal transplantation. The researchers used fecal samples from 3 of the most severely depressed male patients for the transplant and from 3 healthy controls that matched their age and sex.

The rats that received a transplant from the depressed pool showed anhedonia-like behaviors in the sucrose preference test, anxiety-like behaviors in the elevated plus maze, and center aversion in the open field test. These behaviors are considered depressive-like behaviors in the rat model. This study provides support for a direct link between the gut microbiome and depression because the introduction of microbiota from people who suffer from depression leads to more depressive-like behavior. A consideration for this study is that there is some variance in microbiota makeup between humans and rats. Nevertheless, the fact that changes in behavior were seen in a cross-species study, even with more limited areas of overlap, implies the relationship is significant.

Conclusion

Evidence has been presented that supports the theory that there is a direct link between gut microbiome diversity and the onset of depression. Numerous studies have created the foundation for the relationship, and controlled experiments have shown that there is a defined path between the two conditions. While the data points to a direct link between the gut microbiome and depression, more research needs to be done to adequately support a causal relationship. In the future, more research is needed to define the specific microbiota that induces and modulates depression, and researchers should continue investigating the translatability of rodent-model studies. Nevertheless, this preliminary finding offers hope for both depression diagnosis and treatment.

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