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The Effects of Microbes on Human Personality: Anxiety and Depression

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Abstract: The crucial involvement of the gut microbiota in sustaining human health and immune functionality is underscored by numerous studies, highlighting its pivotal role in mediating the intricate gut-brain axis. This underscores the capability of gut microbial inhabitants to modulate neurotransmission, dictate behavioral patterns, and exert further influences. Substantial evidence has converged on the association between gastrointestinal microbial compositions and conditions such as anxiety and depression, implying a regulatory interplay. This discussion examines data from preclinical in vivo studies and clinical literature, including investigations using germ-free animal models, as well as evaluations of therapeutic interventions involving prebiotics, probiotics, synbiotics, and postbiotics. Additionally, it explores the implications of fecal microbiota transplantation (FMT). By employing such diverse methodological approaches, a comprehensive understanding of the gut microbiome's contribution to neuropsychiatric well-being is emerging, underscoring the importance of gut-microbial balance for overall health.

Keywords: gut–brain axis, microbiota, anxiety, depression, probiotics.

1. Introduction

Nowadays, anxiety and depression are on the rise, significantly impacting individuals' lifestyles, well-being, and various aspects of their lives. Studies indicate that these conditions may soon become the most prevalent global health issue, posing a substantial challenge to society [1]. The incidence rate has risen to 3152.9/100000, an increase of 27.6%, with 246 million people suffering from depression and anxiety in 2020, according to *The Lancet*. But there are only a quarter of them received treatment. Moreover, the rise in depressive symptoms contributed to a surge in adolescent suicides between 2010 and 2015, while in China, 200,000 people died from drug-related issues [2]. Furthermore, research has demonstrated that tolerance emerges during follow-up care; recurrent administration of the same medication to the same patient may result in decreased efficacy. It is estimated that up to 35% of people suffer from treatment-resistant depression [3]. Thus, it is imperative to delve into innovative treatment options aimed at preserving the overall well-being and quality of life for individuals suffering from depression. But the latest research shows that diet, nutrition, and some bacteria are linked to depression and anxiety. Modifying these factors may be effective in treating or preventing these conditions. It has been reported that gut microbiota would affect brain and mental health in a variety of ways, such as the vagus nerve, microbial regulation of neuroimmune signaling, microbiota-mediated tryptophan metabolism, microbial control of neuroendocrine function, and

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microbial production of neuroactive compounds [4]. The purpose of this review is to consolidate information pertaining to the involvement of the microbiota-gut-brain axis in the development of neuropsychiatric and neurological disorders, specifically depression and anxiety. It endeavors to establish a contemporary framework for this swiftly progressing research field. The review commences with an introduction to the microbiota-gut-brain axis, followed by an assessment grounded in studies employing germ-free animals, investigations of microbiota composition, pertinent human microbiome research, and explorations of probiotics, prebiotics, and antibiotics. Lastly, the review delves into the significance of fecal microbiota transplantation in this context.

2. Epidemiology of Depression and Anxiety and Associated Risks and Impacts

2.1. The Brain-Gut Axis in Anxiety and Depression

Many investigative undertakings have shed light on the central role of the gut-brain axis in initiating and perpetuating depressive and anxiety conditions. This intricate system fosters a reciprocal dialogue between neurological and gastrointestinal realms, permitting the circulation of vital information indispensable for maintaining holistic mental well-being.

The gut is associated with the central nervous system (CNS) and includes the enteric nervous system (ENS), sympathetic and parasympathetic autonomic nervous system (ANS) branches, as well as neuroimmune and neuroendocrine signaling pathways [4]. These control the action of the gut-brain axis and the information it transmits. And there are a few other molecules such as γ-aminobutyric acid (GABA) neurotransmitters, secondary bile acids, short-chain fatty acids, and metabolites produced by the microbiota that regulate these mechanisms [1]. Abnormal gut-brain axis is associated with neuroinflammation and changes in the permeability of the blood-brain barrier (BBB) caused by intestinal dysbiosis or intestinal disorder. Animal studies have shown that when the normal gut microbiota is injured or absent, BBB becomes more permeable, which weakens its protective properties and leads to abnormal behavior and outcomes [5]. Furthermore, certain hormonal and humoral cues can exert a notable impact on this matter, thereby contributing to the overall phenomenon.

2.2. Relationship Between Microbiota and Depression and Anxiety

The gut microbiome is highly diverse, with certain microorganisms contributing to overall health, while others may be associated with mental disorders.

Microorganisms exist in the human gut in a symbiotic relationship, with Bacteroidetes and Firmicutes being the two most prominent bacterial phyla in healthy individuals [7]. The microbiota can influence the synthesis and metabolism of neurotransmitters and can also produce these neuroactive substances on its own. Many enzyme activities use the metabolites generated by the gut microbiota as cofactors and substrates [1]. It has been found that in patients with anxiety disorders, the abundance of Prevonella has increased, while the abundance of Firmicutes and Bacteroidetes and Faecalibacterium has been significantly decreased [8]. Several studies have shown that there are up to 4 phyla and 16 bacteriological families between healthy humans and patients with major depressive disorder, and α diversity is relatively reduced [8].

2.3. Blood-brain and Epithelial-intestinal Barriers

The common denominator between BBB and epithelial-intestinal barriers is that both possess specific, specialized vascular barriers. The main component of the BBB is the capillary endothelial cell (EC), which is an important component of the neurovascular unit [4]. It is sealed by intracellular tight junction proteins, which guarantees the functionality and integrity of the BBB. When intact, BBB can

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prevent microbiota colonization at a critical time in the development of the newborn baby's brain and shields the brain from exposure to bacterial metabolites and new molecules during metabolic transitions [9].

2.4. Risks and Effects Associated with Depression and Anxiety

Depression and anxiety disorders pose numerous hazards, stemming from a multitude of contributing factors encompassing biological predispositions, genetic makeup, individual personality characteristics, as well as social, economic, and lifestyle influences. Furthermore, the presence of a chronic health condition or persistent ill-health frequently elevates the risk of developing these disorders. Consequently, they may give rise to a range of complications, including hepatic dysfunction, uremic conditions, and sleep disturbances, among others. Several investigations have delved into the determinants of depression and anxiety prevalent among student populations, examining a multitude of risk factors. These variables include only child status, age, grade, and ethnicity, academic stress, smoking addiction, alcohol abuse, and family economic status [1].

3. Clinical models are Used to Study Anxiety and Depression

3.1. Germ-free (GF) Mouse Studies

Bravo's research indicates that vagotomy inhibited the influence of Lactobacillus rhamnosus on brain chemistry and reduced depressive-like behaviors in mice, particularly those induced by stress. After lipopolysaccharide (LPS) treatment, subdiaphragmatic vagotomy (SDV) was demonstrated to decrease depression-like symptoms, pro-inflammatory cytokine levels, synaptic protein expression, and abnormal gut microbiota composition in mice [4]. Scientists have investigated the influence of the probiotic, Lactobacillus rhamnosus, on neural functioning by employing mouse models that mimic depressive states. This approach allows for a detailed examination of how the probiotic may modulate neurological processes relevant to depression. One study found a link, either dependent or independent, between vagal signaling and differences in the c-Fos protein in specific brain regions [1]. Acquired powerlessness Acetic and propionic acid levels in the feces of sensitive rats were much lower than those of the control group. The incapacity to learn The relative abundances of Lactobacillus, Anaerofustis, and Clostridium cluster III were considerably higher in robust rats. It's interesting to note that antibiotic-induced gut dysbiosis in mice was linked to resistance to persistent social defeat stress [4].

3.2. Human Research

Many clinical studies have found that patients frequently experience symptoms such as vomiting, diarrhea, and nausea. According to the literature, Prevonella, Clostridium, Bacteroidetes, Klebsiella, and Streptococcus are more abundant in such patients, while Firmicutes, Faecalibacterium spp., and the overall α diversity of the microbiota are reduced [6]. In addition, a study of 198 Spain individuals found that Simpson’s diversity was found to be lower in patients with anxiety [10]. And, a cross-sectional study of 5,558 Chinese found that women infected with H. pylori had a significantly higher risk of depressive symptoms, while men did not [11]. Women are more prone than men to have anxiety and depression, which could be related to the association between H. pylori and cancer [12]. Estradiol-degrading bacteria are higher in women [13]. Also, studies have shown that 30.8% and 21.7% of older adults with FC suffer from depression and anxiety, respectively [14]. And the proportion increased with the severity of constipation symptoms (depression mild: 17.5% vs. moderate: 28.2% vs. severe: 46.0%, $p = 0.003$; Anxiety was mild: 8.8% vs. moderate: 21.8% vs.

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severe: 33.3%, p = 0.005) [14]. Spearman's coefficient was shown in three dimensions, and abdominal symptoms were positively correlated with depression and anxiety.

4. Potential Therapies for Depression and Anxiety: Pros and Cons

Driven by societal advancements, the field of depression and anxiety treatment has witnessed a remarkable surge in the development of synthetic medications. However, their efficacy and mechanisms of action vary significantly due to individual physiological differences, exhibiting a highly personalized nature. Furthermore, scientific research has conclusively demonstrated that specific components derived from food can pave new avenues for the prevention and treatment of mental illnesses by modulating the gut microbiota. These non-pharmacological approaches, encompassing dietary modifications, probiotic supplementation, prebiotic utilization, micronutrient intake, and cutting-edge fecal microbiota transplantation techniques, have all been validated as effective strategies for restoring gut microbial diversity. Subsequent chapters will delve into the specific implementation pathways of these strategies and their multifaceted impacts on individual health, aiming to provide a more comprehensive and personalized therapeutic perspective within the realm of mental health.

4.1. Treat by Improving Your Diet

Adopting salutary dietary practices can alleviate depressive manifestations, not only in individuals diagnosed with depression but also in the general population, promoting balanced mental well-being. Observational studies have shown that healthy eating patterns are associated with a lower risk of depression [15]. However, it should be acknowledged that depression can lead to poor diet. Stricter adherence to healthy dietary patterns, including healthy/cautious, Eastern Mediterranean, and pro-vegetarian diets (i.e., plant-based foods are higher than animal-based foods) can reduce the likelihood of disease [15]. As the quality of the diet improved, a lower incidence of depression was observed. This improvement in diet also influences the intestinal flora, which may be one of the reasons for alleviating depressive symptoms.

4.2. Probiotics

Prebiotics represent distinct nutrients which foster the growth and functionality of beneficial gut microbiota, thereby enhancing their overall performance. Dietary prebiotics, such as fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), promoted the growth of beneficial bacteria like B. longum in young, healthy volunteers and reduced the stress-induced activation of the hypothalamic-pituitary-adrenal axis [6]. After being given GOS, rats showed less anxiety and depressive-like behavior brought on by lipopolysaccharides. Crocin-I increased the amounts of short-chain fatty acids and the makeup of the gut microbiota [11].

4.3. Prebiotics

In the prebiotic study, an assessment was conducted on various compounds, notably Bimuno-galactooligosaccharide (abbreviated as B-GOS), fructooligosaccharide® (FOS), generic GOS, as well as short-chain fructooligosaccharide (scFOS), all of which exhibited the capability to mitigate the activation of the hypothalamic-pituitary-adrenal axis, a physiological response to stress [16]. Specifically, GOS administration to rats was found to alleviate anxiety- and depression-related behaviors, which were previously elicited by lipopolysaccharides [17]. Nevertheless, when comparing the prebiotic intervention group to the control group, no significant disparity was

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discernible, and this pattern persisted in subsequent sensitivity assessments, focused solely on FOS and scFOS, in relation to depressive and anxious manifestations, respectively.

4.4. Trace Element

Trace elements, which are essential for both human and microbial life, play a key role in modulating the composition and functionality of the intestinal flora. Studies reveal that mice subjected to magnesium-restricted diets underwent alterations in their gut microbiome, which correlated with depressive-like behaviors [18]. Notably, iron, a crucial nutrient for many bacterial species, can influence gut microbiota diversity through dietary intake [19]. Furthermore, individuals suffering from depression exhibit lower iron levels compared to healthy counterparts, suggesting that iron deficiency may impair neurotransmitter synthesis, a critical factor in the biological mechanisms underlying depression.

4.5. Fecal Microbiota Transplantation (FMT)

The process of FMT, which stands for fecal microbiota transplantation, has garnered recognition for its ability to restore gut microbial diversity and thereby address patient-specific imbalances, accomplished by transplanting the microbiota of healthy subjects into the patient's intestinal tract. Notably, studies have demonstrated a reduction in anxiety and depressive symptoms among mice models, subsequent to the introduction of fecal microbiota from healthy donors [1]. Currently, FMT stands as a prevalent therapeutic modality for managing both gastrointestinal and neuropsychiatric conditions, as supported by numerous studies [20]. However, it is imperative to underscore the risks associated with sourcing fecal microbiota from unhealthy individuals, which could result in adverse reactions or undesirable side effects [4]. Consequently, the decision to employ FMT therapy necessitates meticulous evaluation and the implementation of additional safety measures to ensure its appropriate application.

4.6. Advantages and Limitations of Gut Microbiome Therapy

These modalities of treatment possess the capability to rectify select types of microbial imbalance, fostering a microbiota conducive to health. The efficacy of these interventions has been substantiated via rigorous experimentation encompassing both animal models and human trials, revealing the potential for long-term disease resolution. Nevertheless, compared to conventional therapies, this approach necessitates a prolonged timeframe for observable outcomes, and it is pertinent to note that a subset of microbial species may exhibit adverse effects in individuals with comorbidities or genetic predispositions.

5. Conclusion

Numerous investigations have delved into the influence of gut microbiota on depression and anxiety disorders, recently uncovering its capacity to modulate mental well-being via the gut-brain axis, thereby revealing potential avenues for diagnosis and therapeutic interventions. The composition of the gut microbiota is very diverse, many of which are associated with psychiatric disorders. Many studies and surveys have proven that the number of people affected is increasing year by year. Besides, owing to individual variations, the diversity and abundance of microbial species within each human body also differ significantly, making targeted treatment modalities and precise identification methods particularly important. Consistent findings from epidemiological, experimental, and clinical investigations highlight the protective and therapeutic effects of dietary modifications, in conjunction with the modulation of probiotics, gut microbiota, trace element supplementation, and prebiotic

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utilization, in alleviating anxiety and depression. Nevertheless, the current landscape of experiments and research predominantly relies on rodent models, with human-based models underrepresented. Given the critical need for increased diversity, specificity, and high-quality clinical trials with larger sample sizes in the future, further exploration of blood-brain barrier permeability, inflammatory processes, and related mechanisms is warranted. Additionally, these efforts should strive to evaluate and establish appropriate dosages and the efficacy of microbial restoration therapies, ensuring their rational and effective application.

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