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Gut Microbiota and Anxiety: An Exploration of Key Findings

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Abstract

There is a growing body of evidence linking the intestinal microbiota with anxiety disorders. Studies using germ free (GF) rodent models have demonstrated that bacterial colonization of the gut is crucial to the development of the central nervous system (CNS), enteric nervous system (ENS), and the hypothalamic-pituitary-adrenal (HPA) axis. Furthermore, evidence points towards the important role of gut microbiota in the induction of the anxiety response, with a disrupted gut microbiome leading to aberrations in stress-related behaviors and anxiety. In human subjects, ingestion of probiotics has been shown to reduce anxiety symptoms, thereby further strengthening the link between gut microbiome and anxiety. In this article, we review studies examining the relationship between gut microbiota and anxiety, and discuss proposed mechanisms and future direction of research.

Keywords: Central nervous system; Anxiety; Depression; Microbiota

Introduction

The human body serves as the natural ecosystem for bacteria and other microorganisms, with the entirety of these microorganisms termed the human microbiota and the entirety of genes from this collective termed the human microbiome. The human gut is initially sterile; microbial colonization begins immediately after birth and is influenced by the route of delivery, maternal transfer, diet, environmental factors, and antibiotic usage [1]. In adulthood, the phyla Firmicutes and Bacteroidetes, followed by Actinobacteria and Proteobacteria, are predominant in healthy and balanced gut communities [2]. Disruptions of this critical balance are implicated in the etiology and pathogenesis of a wide range of medical conditions, including autoimmune disorders, allergies, systemic infections following cancer chemotherapy, and obesity [3-6]. There is now increasing evidence of a brain-gut-microbe connection, with results from germ free (GF) animal models and probiotic studies supporting a link between gut microbes and anxiety. Here we review the pivotal studies in the field.

Studies using germ free (Gf) rodent models

Using GF rodent models, in which the rodents are born and raised under sterile conditions and therefore have no commensal intestinal microbiota, researchers have shown that bacterial colonization of the gut is central to the development and maturation of both the central nervous system (CNS) and the enteric nervous system (ENS) [7]. The absence of microbial colonization leads to both altered neurotransmitters (NT) and altered gut sensory and motor functions, with abnormalities corrected when microbial colonization is reestablished [8,9]. Gut microbiota also influences the development of the hypothalamic-pituitary-adrenal axis (HPA axis), with acute stress inducing an exaggerated release of corticosterone in GF mice that is partially normalized by bacterial colonization at six but not eight weeks, suggesting a critical period in which the brain is sensitive to signals from the gut [10].

Given the impact of the microbiota on HPA axis responsivity, it has been postulated that stress-related behaviors and anxiety are also influenced by the microbiota. Consistent with the exaggerated stress response in GF animals, the absence of gut microbiota in rodent model exacerbates the neuroendocrine and behavioral response to acute stress [11]. Studies have shown that GF mice exhibit a reduction in basal levels of anxiety like behaviors as compared to mice with a normal gut microbiota [8,12,13]. Moreover, anxiety-like behaviors of GF mice are unaffected by maternal separation, pointing towards the role of the gut microbiota in the induction of the anxiety response associated with early life stress [14].

Interestingly, GF mice exposed to gut microbiota early in life display anxiety like behaviors similar to mice with normal gut microbiota, suggesting that microbial colonization may initiate signaling mechanisms affecting neuronal circuits for anxiety [8]. This normalization does not occur with microbial reconstitution in adulthood, thereby pointing towards a critical period early on in which the anxiety response is imparted [8,12]. Furthermore, even if a normal gut microbiome is initially present, a substantial bacterial reduction can influence key neuromodulators that contribute to altered cognition and anxiety response, as evidenced with antibiotic administration in a rodent model [15].

Probiotics

Probiotics are living nonpathogenic microorganisms which benefit the host organism's health, with ingestion of probiotics as a therapeutic manner of manipulating the microbiota composition. The mechanisms by which probiotics exert their influence on the brain are not yet fully understood, but likely involve multiple pathways between brain, gut, and immune system.

Lactobacillus and *Bifidobacterium* species are key components in probiotics, and treatment with beneficial strains of these species have anxiolytic effects and can normalize behavioral phenotypes in animal anxiety models [16]. The anxiolytic effects may involve activating vagal pathways for gut-brain communication [17]. *Lactobacillus* and *Bifidobacterium* species also produce metabolites, including neuroactive substances like GABA, which may play a role in microbiota-gut-CNS signaling [18]. Probiotics may also exert their effects by modulating HPA axis stress response, with *Lactobacillus farciminis* preventing gut

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leakiness and attenuating HPA response to an acute stress in rats [19]. Another proposed mechanism is that probiotics lead to the increased production of free tryptophan, which in turn increases serotonin and thereby improves symptoms [20].

Discussion

In humans, consumption of a probiotic drink containing *Lactobacillus* reduced anxiety, as marked by lower Beck Anxiety Inventory (BAI) scores, in subjects with chronic fatigue syndrome [21]. Intake of *Bifidobacterium longum* did reduce depression and increase quality of life, but did not reduce anxiety in subjects with irritable bowel syndrome [22]. However, in another study, administration of the prebiotic trans-galactooligosaccharide, which promotes the growth of *Lactobacilli*, did result in decreased scores on the anxiety subscale of the Hospital Anxiety and Depression scale (HADS-A) [23]. Similarly in healthy human subjects, there was a decrease in HADS-A scores following ingestion over a 30 day period of formulation consisting of *Lactobacillus helveticus* and *Bifidobacterium longum* [24]. In a six-month study that looked at 42 subjects with stress and exhaustion, ingestion of a probiotic multivitamin led to an overall 40.7% improvement in stress [25]. Moreover, consumption of fermented foods that contain probiotics may have a protective effect against social anxiety symptoms in those at high genetic risk for social anxiety disorder [26].

Although the above studies have found an association between probiotic consumption and decrease in anxiety/stress, the results are far from conclusive. We must underscore that current evidence does not support the use of probiotics as a treatment for anxiety. The evidence base for probiotics is limited, and more rigorous studies, especially interventional studies, are needed. Furthermore, it may be advantageous at the current time for research to be directed towards further clarification of the relationship between gut microbiota and anxiety and the mechanistic underlying. Once more insight into this relationship is gained, then that will pave the way for a better understanding of the role of microbial reconstitution.

Conclusion

Anxiety disorders are the most common class of mental disorders present in the general population, carrying with it significant emotional, social, and economic strain. There is an increasing body of evidence demonstrating the clinical importance of gut microbiome and gut-brain interactions in the development of psychiatric disorders. Evidence from GF animal models and probiotic studies point towards a connection between disrupted gut microbiota and anxiety. However, this field is in its early stages and further studies are needed to elucidate the precise nature of this relationship and the underlying mechanisms. First and foremost, it remains to be determined whether disruptions in gut microbiome are secondary to altered neural regulation of gut activity or if it signifies primary aberrations that then influence brain development and function. Moreover, although there is emerging evidence on how reconstitution of beneficial microbes may be beneficial in anxiety disorders, more definitive studies are needed to further examine whether this is indeed the case. As we gain more understanding, new therapeutic approaches may become available to help diminish the burden of this disorder.

Conflict of Interest

Dr. Ding declares that she has no conflict of interest.

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