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Gut Feelings: A Role For the Intestinal Microbiota in Anorexia Nervosa?

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Anorexia nervosa (AN) continues to perplex, and new lenses with which to view the disorder are essential to advancing understanding and enhancing treatment. Although a fundamental first step in treatment, few clinical trials exist that explore how best to renourish individuals with AN, and treatment approaches typically are based on clinical opinion or guidelines.¹ Moreover, gastrointestinal effects of refeeding are uncomfortable, distressing, and painful, resulting in low treatment acceptance and high dropout.

Humans coexist with numerous diverse microbial communities, or microbiotas, living in and on the human body. The intestinal microbiota refers to living organisms, including prokaryotes, eukaryotes, archaea, and viruses, while the microbiome refers to the cumulative genomes of these organisms. Although each person has a unique microbiota, a core set of microorganisms is common across individuals. The environment, including long-term dietary patterns, exerts profound influence on the intestinal microbiota. Short-term dietary changes can also induce measurable microbial shifts.

Compelling evidence that the intestinal microbiota regulates key features of AN, including weight regulation, energy metabolism,² anxiety, and depression,³ provides a strong rationale for exploring the role of this complex microbial community in AN. Yet the functional role of the intestinal microbiota in the maintenance of and recovery from AN has not been explored. Based on the existing literature, it is logical to posit that changes to gut microbial communities associated with extreme weight loss may perpetuate and contribute to AN via direct effects on weight and mood. Defining alterations and functional effects of AN intestinal microbiotas on adiposity and behavior could provide new mechanistic insights into this perplexing illness and guide new treatment paradigms.

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A dysbiosis or microbial imbalance in the intestinal microbiota exists in AN patients

A small culture-based study of a stool sample from an AN patient at hospital admission identified 11 completely new bacterial species in the Firmicutes (n=7), Bacteroidetes (n=2), and Actinobacteria (n=2) phyla, which may suggest distinct characteristics of the intestinal microbiota in AN.⁴ However, further research is needed to investigate whether these new species are uniquely associated with AN. Moreover, a molecular-based study analyzing the intestinal microbiota of nine AN patients found increased levels of the archaeon *Methanobrevibacter smithii*.⁵ Although intriguing, this study was cross-sectional and used a narrow approach (quantitative PCR of specific bacterial taxa) to determine the abundances of a limited number of microbial groups (n=4). Given that the intestinal microbiota encompasses 300–1000 different microbial species, a more comprehensive characterization of the intestinal microbiota in AN, how it changes following treatment, and how it differs from healthy controls is warranted. Exploration of longitudinal changes in the intestinal microbiota in AN patients over the course of medically supervised weight restoration would provide new insights into how current AN treatment impacts enteric microbes and how microbial shifts may contribute to adipose distribution and behavior.

The intestinal microbiota influences adiposity in humans and animal models

Consistent evidence implicates the intestinal microbiota with excessive accumulation and storage of fat in humans. Additionally, in mice, obese intestinal microbiotas are more effective at extracting calories from food and stimulating host accumulation of fat than microbiotas of lean mice.⁶ Transfer of microbiota from mouse models of diet- or genetically-induced obesity to germ-free (GF) mice is sufficient to stimulate increased adiposity and metabolic dysfunction. Similarly, fecal samples transplanted to mice from obese adult humans transmit obesity-associated phenotypes via the intestinal microbiota. Given that AN is marked by extreme weight dysregulation and is treated initially by weight restoration, exploring the functional impact of a dysbiotic intestinal microbiota on adiposity in AN is a logical and critical step toward better understanding of AN pathophysiology and treatment response.

The intestinal microbiota influences behavior in animal models

A majority of individuals with AN will have a lifetime history of anxiety or depression. Animal models provide evidence that enteric microbes significantly influence both anxiety and depression. For example, infection with a pathogenic microbe increases anxiety-like behavior, and GF mice exhibit reduced anxiety-like behavior that is reversed upon reconstitution with a gut microbiota. In a clinical trial, healthy human volunteers who consumed a mixture of probiotics exhibited reduced anxiety and depression in comparison to placebo. There are many possible mechanisms involved; however, Bravo *et al.* (2011) suggest that a naturally occurring enteric microorganism used as a probiotic impacts behavior via the vagus nerve and gamma-aminobutyric acid (GABA) expression in the brain.

The investigation of the specific enteric microbes that influence anxiety and depression in AN has never been attempted. The centrality of anxiety and depression in AN, and the demonstrated role of the intestinal microbiota on these traits, support research to identify whether microbial shifts in AN patients correlate with anxiety and depression measures and if they confer anxiety and depression to GF mice.

The intestinal microbiota is a valid intervention target

Studies involving transplantation of intact uncultured microbiotas from healthy humans to individuals with *Clostridium difficile*-induced colitis or patients with metabolic syndrome have provided proof-of-principle that the intestinal microbiota represents a valid therapeutic target for treating or preventing disease. These findings suggest the possibility of use of fecal microbial transplants beyond the treatment of *C. difficile* and metabolic syndrome, but this research is in its infancy and the mechanism by which these transplants (via enema or capsule) induce a beneficial outcome is unclear. Supporting this concept, a probiotic originally isolated from the intestinal microbiota of a healthy individual (*Lactobacillus rhamnosus* JB-1) reduced anxiety- and stress-related behavior in mice via modulation of GABA expression. These biological and behavioral effects were not seen in vagotomized mice, illustrating the critical role of microbe-gut-brain communication. Thus, an enteric microbe, originating from the intestinal microbiota, is known to regulate behaviors that are prominent in AN. Moreover, probiotic-based therapies have shown that *Lactobacillus rhamnosus* and *Faecalibacterium prausnitzii* can protect against intestinal epithelial barrier function abnormalities. Indeed, increased intestinal permeability or a “leaky gut” has been demonstrated in an activity-based mouse model of AN. Given the ability of enteric organisms to regulate gut barrier function, it is possible that one of the mechanisms in which a dysbiotic intestinal microbiota leads to AN is via the dysregulation of this barrier. Identifying microbes within the intestinal microbiota of AN patients associated with specific AN traits (weight regulation, anxiety, and depression) that are transmissible to GF mice would provide a rationale to develop new, microbiota-based treatments for this disorder.

Our “idea worth researching” would pioneer the combination of large scale 16S rRNA gene sequencing-based studies of intestinal microbiotas in AN with exploration of their functional influence on weight regulation and behavioral traits associated with AN. Correlating the configuration of an individual’s intestinal microbiota with health status is a fundamental first step in testing for a causative role of enteric microbes in AN. A unique challenge for this research is the inability to compare individuals with AN to similarly malnourished individuals who do not have AN or other medical conditions that result in malnutrition. This does not preclude other informative designs that could, for example, explore whether the presence of specific enteric microbes are associated with successful weight retention after renourishment.

A major challenge for current microbiome-related research is how to move from observational to functional and mechanistic studies that dissect how these microbes impact a host’s biology. One option is transplanting an intact uncultured human intestinal microbiota (from feces) from AN patients into GF mice and measuring anthropometric, metabolic, and behavioral changes that occur along with the composition of the intestinal microbiota. This

would test the ability of donor microbiotas to functionally impact AN-related phenotypes (i.e., weight regulation, anxiety, and depression) in the recipient animals. Identifying enteric microbes that have a potential detrimental or beneficial impact on weight regulation and behavior in AN patients would generate target microbes that can then be studied further on a platform that enables the investigation of host-microbe interactions, namely gnotobiotics.

Novel interventions for AN are essential. Microbiota-modulating strategies could comprise a significant therapeutic advance in treatment of AN. Our incomplete understanding of the pathophysiology of AN has hindered the development of novel, safe, acceptable, and effective treatments. Concerted attention to this area could identify bacterial taxa whose promotion or elimination would improve the efficiency of therapeutic weight restoration, as well as the psychological and physical treatment experience of patients. We need new information about the biology of AN at a microbial level to inform innovative therapies targeting enteric microorganisms, which may fundamentally alter the way we understand and treat AN. This is, of course, just a first step, as the role of the intestinal microbiota in the development, maintenance of, and recovery from bulimia nervosa, binge eating disorder, and other eating disorders presentations is the next microbial frontier.

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