Biological Psychiatry

Commentary

Targeting the Microbiome for Mental Health: Hype or Hope?

Jane A. Foster

In the past decade, the microbiota-gut-brain axis has moved to the forefront of neuroscience and psychiatry research. Curiosity about how our bacteria influence health and disease is not limited to scientists and the medical community; the public and the media are completely engaged—it would be difficult to find a stakeholder group related to mental health that has not jumped on the bandwagon. The momentum has been driven primarily by studies in animal models. Evidence is accumulating to show that microbiota influence brain function and behavior, particularly brain systems related to mood and emotions (1). In this fast-moving field of research, the key questions remain: is the growing attention to microbes and mood hype—or is there hope and opportunity for identifying novel approaches to improve mental health?

Microbiota cover all surfaces of our body and include bacteria, viruses, fungi, parasites, and protozoa; however, neuroscience and psychiatry research has focused predominantly on gut microbiota. Much of the support for the concept that microbiota-brain communication is essential to brain health has stemmed from studies that manipulate the microbiota in animals. Studies employing germ-free mice that lack all microbes and are raised in sterile environments are numerous and demonstrate that microbiota influence stress reactivity, stress-related behaviors, social behavior, and cognition (2). Along the gut-brain axis, microbiota influence gut barrier integrity, immune function, and the blood-brain barrier and within the central nervous system several signaling systems are influenced, including neurotransmitters, neurotrophins, microglia, synaptic plasticity, and neurogenesis (2). Similar conclusions about microbiota-brain influence can be drawn from studies manipulating the microbiome through other means, including stress, diet, exercise, antibiotics, and more. Together, studies to date clearly have demonstrated that the complex interplay among our commensal bacteria, our body, and our brain are critical to normal healthy brain function and understanding these interactions may provide new avenues for interventions to improve outcomes in psychiatric disorders.

The potential of "psychobiotics" as interventions in psychiatry is of great interest. Psychobiotics are "live bacteria (probiotics) or other products (prebiotics) that when ingested confer mental health benefits through interactions with commensal gut bacteria" (3,4). The potential benefits of probiotics is evident in animal studies (3,5) and to a more limited extent in human studies in healthy individuals and in clinical populations (3). Prebiotics are dietary products that when consumed can be fermented by commensal gut bacteria and alter microbiota composition or function (3,6). Short-chain fatty acids (SCFAs) including acetate, propionate, and butyrate are metabolites that are products of commensal fermentation (7). SCFAs produced by gut bacteria influence other commensals and are important to gut physiology, but they are also part of microbiota-host signaling systems that extend beyond the gut (7). A few studies have demonstrated beneficial effects on health and disease following prebiotic administration (3). In this issue of *Biological Psychiatry*, Burokas *et al.* (8) explore the beneficial effects of prebiotics, fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) on behavior in healthy mice and further investigate the ability of prebiotics to counter the impact of stress in mice. In the study, 10 weeks of prebiotic administration (FOS alone, GOS alone, or a combination of FOS + GOS) in healthy male adult mice resulted in changes in the composition of gut microbiota and related changes in SCFAs (8). The authors highlight some key bacteria taxa that are shifted in response to prebiotics including *Akkermansia*, which has been implicated in improved metabolic health in overweight and obese individuals in response to a dietary intervention (9). A targeted approach to link specific taxa to neurobiological processes is critical to identify targets for development of novel dietary approaches or for monitoring the impact of different interventions on mental health. Consensus is building in relation to the specific bacterial taxa that may have functional links to mental health; however, the current standard practice that examines relative abundance at a single cross-sectional time point (most studies) limits the generalizability and reproducibility of the findings. For example, in the current study, the relative abundance of *Lactobacillus* and *Bifidobacterium*, notably the two most prominent probiotics on the market with demonstrated beneficial effects in animal and clinical studies (3), showed reduced relative abundance following prebiotic administration, but no differences in abundance when measured by polymerase chain reaction. This is more of an analytical issue than a technical issue, emphasizing the need for analytical tools that consider the sequencing origin as well as the compositional and multivariate nature of 16S datasets.

The link between manipulations of microbiota and anxiety-like behavior is the most frequent and robust observation in animal studies (5). Within the battery of behavioral tests examined by Burokas *et al.* (8), prebiotic treatment reduced anxiety- and depressive-like behaviors in healthy mice. Additionally, prebiotic administration during chronic stress normalized the effects of stress on behavior, neurochemistry, and the stress axis. These findings add to the body of literature that supports a role for microbiota-brain communication in mood and emotional domains (8), and they demonstrate that dietary interventions may have potential in mental health. Changes observed in the stress axis and central nervous

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system–related systems support the interpretation that behavioral changes occurring following prebiotic administration are a result of microbiota-brain related signaling. To identify the molecular mechanisms that mediate beneficial effects of prebiotics, the authors examined SCFAs, a byproduct of prebiotic administration, and suggest that changes in SCFAs may mediate the impact of prebiotics on brain systems and behavior. This is an important contribution and is of great interest to the field. SCFA levels in the current study were associated with neurochemistry and behavior; however, the association analysis was general in nature and provided only an omnibus look at the complex interplay of SCFAs and many outcomes related to the gut-brain axis (8). Changes in SCFAs were associated with several outcomes, but it was not determined if these associations are the result of local effects of SCFAs or remote effects. It is important to note that there is specificity in the nature of bacterial production of SCFAs (7), and although the evidence suggests that these metabolites may mediate some of the beneficial effects of diet interventions, additional approaches are needed to directly asses the source and action of SCFAs in animal and human studies.

As noted above, probiotics on the market and showing beneficial effects on mental health and brain function are limited in number. Prebiotic intervention is attractive, as the impact could involve several different taxa (as seen here) and may be effective in a broader range of individuals than probiotics are. Interestingly, in many of the outcomes measured by Burokas *et al.*, a combination of FOS and GOS had a greater impact than either prebiotic alone. The authors suggest that this might have been due to "a broader range of bacterial stimulation," which is likely, and it is plausible that these effects are directly related to changes in microbiota composition and function, as beneficial effects of a cocktail approach have been observed in studies using probiotics (5). It is important to translational efforts linked to the gut-brain axis that we determine if the best therapeutic strategy for these interventions is a cocktail rather than a single prebiotic or probiotic.

Overall, the study by Burokas *et al.* provides convincing evidence for beneficial effects of prebiotics on microbiota-brain systems in healthy mice and in stress conditions. While the evidence is convincing to most, there are skeptics and critics who question the importance of these animal studies; hence there is a clear need for translational approaches to demonstrate that the early findings in animal models are representative of microbiota-brain communication and its impact in healthy and clinical populations.

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Article Information

From the Department of Psychiatry & Behavioural Neurosciences, McMaster University, Hamilton, Ontario, Canada.

Address correspondence to Jane A. Foster, Ph.D., Department of Psychiatry & Behavioural Neurosciences, McMaster University @ St. Joseph's Healthcare, 50 Charlton Avenue East, T3308, Hamilton, ON L8N 4A6, Canada; E-mail: jfoster@mcmaster.ca.

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