The effects of probiotics on mood and emotion

Lindsey Kane; Julie Kinzel, MEd, PA-C, DFAAPA

ABSTRACT

Preliminary research in humans and rodents demonstrates that various probiotic formulations of *Lactobacillus* and *Bifidobacterium* have a clinical and neurochemical anxiolytic effect on the central nervous system (CNS). Further research is warranted to more extensively examine the theorized connection between the gastrointestinal tract and the CNS; however, initial evidence suggests probiotics affect various mechanisms of the gut-brain connection that modulate anxiety-like behaviors. This article describes the wider-reaching effects of probiotics, specifically related to behavior and brain function.

Keywords: probiotics, microbiome gut-brain axis, gut microflora, anxiety, *Lactobacillus*, *Bifidobacterium*, behavior

In recent years, public and clinical interest in probiotic formulations and their role in gastrointestinal (GI) health has increased. Indeed, these microorganisms are known to have beneficial effects in the treatment of antibiotic-associated diarrhea, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other GI-related disturbances (see "Current and future uses of probiotics" in this issue).[1-4] However, more recent research is beginning to identify relationships and communication between the GI tract and central nervous system (CNS) function, specifically with regards to anxiety and stress.[5] Studies have highlighted a link between GI tract infection with pathologic bacteria and long-term GI inflammation with anxiety-like behavior in humans and symptoms analogous to IBD in mice.[6-9] If probiotics have a positive effect on the human GI tract, could they affect the CNS and emotional behavior?

An increasing number of studies have explored the effects probiotic ingestion has on anxiety and depressive-like behaviors in rats and humans.[1,10-13] Studies have examined probiotics' effect on neurotransmitter signaling and neuronal activation in the brain, as well as modulation of hormones and other chemicals in the body such as cytokines.[10]

At the time this article was written, **Lindsey Kane** was a student in the PA program at Drexel University in Philadelphia, Pa. **Julie Kinzel** is an assistant clinical professor in the PA program at Drexel University.
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This article focuses on the two-way communication between the CNS and GI tract, physiologic and chemical effects of probiotics on anxiety, clinically observed effects of two common probiotic formulations on mood, and where future research on probiotics is headed.

THE MICROBIOME GUT-BRAIN AXIS

The microbiome gut-brain axis postulates that although neural signals can control GI function, signaling from the gut microbiota also can affect neurologic functioning. This idea is called *bidirectional signaling*.[8,14] Examples of brain-to-gut signaling include the roles stress and other psychological factors have on IBS symptoms and exacerbations and the correlation between emotional stress and functional dyspepsia.[15,16] Now, clinical trials and research are being conducted to identify mechanisms by which gut microflora can communicate and influence CNS functioning.[8,10,11,14,17]

Studies indicate the vagus nerve also plays a large role in the two-way communication of the gut-brain axis. Mice whose guts were treated with pathologic bacteria such as *Citrobacter rodentium* demonstrated a positive correlation between anxious behavior and elevated vagus sensory neuron activation.[9] A second experiment demonstrated that mice undergoing subdiaphragmatic vagotomies exhibited fewer anxiety-like behaviors than their counterparts with intact vagus nerves.[11] Although anxiety-like behavior has been identified in rodents with GI inflammation both with and without an intact vagus nerve, this may prove to be one of multiple pathways responsible for communication from the gut to the brain.[6]

Gut microbiota also are believed to affect the levels of stress hormones released via the hypothalamic pituitary adrenal axis, and probiotics may be able to reverse this response. The idea was conceived when germ-free mice (mice with no microorganisms growing in them, including their gut) showed higher levels of stress hormones such as plasma corticosterone and adrenocorticotropic hormone level when exposed to anxiety-inducing experiments, compared with mice with normal microbiota and mice free from specific pathogens and diseases.[10,11,17] The heightened stress response and high levels of corticosterone hormone were reversible with administration of probiotic strains *Lactobacillus* and *Bifidobacterium*.[1,17] Mice with conventional gut microflora treated with *Lactobacillus* demonstrated decreased corticosterone levels compared with placebo.[11]

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Key points

- Increasing research suggests that probiotics have beneficial effects on mood and cognition, specifically anxiety.
- Preliminary research in humans and rats suggests anxiolytic effects of probiotics on a clinical and neurochemical basis.
- The microbiome gut-brain axis is a complex system of communication between the GI tract and CNS.

PROBIOTICS AND THE BRAIN

To further solidify evidence of the gut-brain axis, changes in brain activity can be seen with GI tract microflora modulation.[3,7] Diagnostic tests such as functional MRIs in humans, and brain sectioning and c-Fos (a marker of neuronal activity) analysis in rats suggest that probiotic ingestion attenuates emotional reactions and decreases activity of brain regions responsible for behavior, mood, viscerosensation, and somatosensation in response to tests focused on measuring brain responses to emotional stimuli.[3,7] These regions include the amygdala, insula, periaqueductal gray, and prefrontal cortex.[3] A separate study conversely demonstrated that mice infected with pathologic bacteria such as *Campylobacter jejuni* exhibited more anxiety-like behaviors and had heightened activation in brain regions traditionally linked to anxiety.[7]

GABA is the major inhibitory neurotransmitter that plays a key role in regulating many psychological processes, including anxiety and depression.[11] Evidence suggests that chronic administration of *Lactobacilli* and *Bifidobacteria* strains can have similar effects as antidepressants on GABA subunits in areas of the brain related to emotion, mood, memory, and somatosensory processing.[11]

This suggests chemical changes in human and rodent brains in response to GI tract microflora; healthy microflora may mitigate emotional and sensory reactions and pathologic bacteria exacerbate emotional reactions.

PROBIOTICS AND MOOD

On a clinical level, studies have demonstrated a change in emotion and mood in both human and rodent subjects with and without mood disorders.[3,12,13,18] Evaluation of human behavior was completed via behavioral testing (examples: Hopkins System Checklist-90 and the Becks Anxiety and Depression Inventory) to monitor change. Both acute and chronic daily administration of probiotic supplements such as *Lactobacillus* and *Bifidobacteria* supplements taken for 8 weeks appeared to improve anxiety scores in patients suffering from chronic fatigue syndrome, and mood in patients with self-reported symptoms of depression.[12,18] Healthy human subjects taking probiotics over the course of 1 month reported decreases in somatization, anger and hostility, anxiety, and depression.[13] Similar studies performed in rodents suggested that probiotics have anxiolytic effects, at one point apparently reversing anxiety-like behaviors demonstrated by mice infected with a parasitic agent in the gut.[6,13] However, not all studies had equal results and many of these studies in humans use different inclusion and exclusion criteria for subject selection in their experiments (healthy patients versus patients with psychologic or medical comorbidities).

The probiotics used in the human trials included *Lactobacillus rhamnosus, L. helveticus, L. casei (strain Shirota), L. bulgaricus, L. lactis, Bifidobacterium animalis,* and *B. longum*.[1,3,11-13,18] The amount of probiotic given to human subjects varied widely from 3 billion colony-forming units (CFUs) to 24 billion CFUs each day.[3,12,13,18] As probiotics are not regulated by the FDA, the concentration and species of probiotics found in yogurt and supplements sold on grocery and pharmacy shelves may vary. Under FDA regulations, labeling also cannot claim that probiotics improve health or treat disease. Further research will be needed to examine the efficacy of probiotics at different concentrations.

CONCLUSIONS

Although clinicians likely are aware of probiotics' roles in supporting GI health, many may not be aware of these more recent investigations. With more than 40 million Americans affected by anxiety, and at least 6% of Americans being prescribed an anxiolytic or antidepressant within the last month, many clinicians encounter patients with psychologic comorbidities.[19,20] A large population stands to benefit from new approaches to anxiety management or new adjuvant therapies, especially given the long-standing safe adverse reaction profile of probiotics.[21] Although the authors do not suggest that clinicians begin to substitute probiotics for traditional pharmacologic or psychologic interventions for anxiety, they should know about the wider-reaching effects of probiotics, specifically related to brain and behavioral function. **JAAPA**

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