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April 2015

The Microbiome and Overall Health Part 4: The Brain-Gut-Microbiota Connection and the Emergence of Psychobiotics

By Stephen F. Olmstead, MD

[This is the fourth in a series of articles about how the gut and the microbiome influence all areas of health. The first in the series appeared in the January 2015 ProThera®, Inc. Practitioner Newsletter. Previous installments have covered the microbiota and obesity and the gut's role in cardiovascular and autoimmune disease. In the coming months, Dr. Olmstead will discuss such topics as the microbiota and gastric health and the gut's connection to the skin.]

THE BRAIN-GUT AXIS

Throughout the millennia and across different cultures, people have long appreciated close connection between the brain and gut. People speak of "gut feelings" and "gut instincts." Anxiety may give someone "butterflies in the stomach," and "having guts" is a way to describe courage. Physiologically, two-way communication between the central nervous system (CNS) and the gut is well established.[1] The term brain-gut axis denotes the totality of information exchanges between the CNS and the gut encompassing all afferent and efferent neural, hormonal, immunological, and nutritional signals. Traditionally, emphasis has been placed on brain-gut neural connections.[2] The gut contains as many neurons as the spinal cord. However, hormonal connections are equally robust. The past decades have focused on the role of the brain-gut axis in gastrointestinal motility and secretions, pain perception, and appetite control. Current research now reveals that most of the communication along the brain-gut axis is from the gastrointestinal system to the CNS and gut activities can modulate emotions, desires, and mood.[3]

THE BRAIN-GUT-MICROBIOTA PARADIGM SHIFT

Awareness of the vast microbial ecosystem inhabiting the gastrointestinal tract has burgeoned over the past decade. Humans are supraorganisms more microbial than primate by many measures.[4-6] The number of microbial cells outnumbers human cells by a ratio of 10:1 and the collective microbial genome, or microbiome, outnumbers the human genome by 100:1. The microbiota reinforces gut barrier function, competitively excludes pathogens, and provides host nutritional support. A healthy gut microbiota is essential for the normal development of the gastrointestinal and immune systems. The microbiome guides the immunologic maturation and modulates immune function throughout life. Evidence is now accumulating that the gut microbiota is necessary for normal CNS maturation and that it impacts neural circuits controlling motor function and anxiety behavior.[6-12] Studies are disclosing the contributions of the microbiome to neurotransmitter pools and its modulation of the hypothalamic-pituitary-adrenal (HPA) axis.[13,14] The brain-gut axis is now seen to include the gut microbiota in the new paradigm of the brain-gut-microbiome axis.

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MICROBIOTA MODULATION OF BRAIN FUNCTION

Animal studies are shedding new light on how the gut microbiota influences brain function.[8,15-17] The principal mechanisms appear to be neuroendocrine and immunological. Studies in mice have found that postnatal microbial gut colonization programs the HPA axis for responses to stress.[15] Germ-free mice have a reduced behavioral, but exaggerated endocrine response to stress characterized by excessive corticosteroid and adrenocorticotropic hormone release compared to control animals with a normal microbiota and no specific pathogens (known as specific pathogen free [SPF] mice). The abnormal stress response can be attenuated with gut colonization with bacteria from SPF animals, and could be completely normalized by administering the probiotic *Bifidobacterium infantis*. In other studies, chronic treatment with probiotic *Lactobacillus rhamnosus* or with a combination of *L. helveticus* and *B. longum* reduced stress-induced corticosterone and anxiety- and depression-related behaviors in mice.[18,19] However, there appears to be a time after which stress responses cannot be normalized by acquiring a normal gut microbiota. It is possible that stress engenders a negative feedback loop involving the brain, HPA axis, and gut microbiota. Stress is known to reduce intestinal populations of *Lactobacillus, Bacteroides,* and *Bifidobacterium* as well as increase *Clostridium* numbers.[20,21] These changes are associated with elevated levels of interleukin-6 (IL-6) and chemokine CCL2 indicating immune activation, which may engender increased stress. Chronic stress also impairs gut barrier function leading to systemic ingress of immune-activating intestinal bacterial cell wall structures such as lipopolysaccharide (LPS).[22-26] Increased intestinal permeability and translocation of LPS has been reported in patients with major depression.[27] In addition to intestinal microbial modulation of CNS responses through the HPA axis and immune system, the gut microbiota generates numerous neurotransmitters. *Lactobacillus* and *Bifidobacterium* species are known to produce γ-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the mammalian CNS.[28] *Lactobacillus* species make acetylcholine, *Bacillus* species generate dopamine, *Bacillus, Escherichia,* and *Saccharomyces* species produce norepinephrine, and *Candida, Streptococcus, Escherichia,* and *Enterococcus* make serotonin. *B. infantis* modulates the kynurenine metabolic cascade that generates over 95% of the available peripheral tryptophan and has been shown to increase both kynurenine and tryptophan plasma levels in rats.[30] *L. acidophilus* increases the expression of gut epithelial opioid and cannabinoid receptors and favorably modulates visceral pain perception in both animal and human studies.[31,32] Many of the effects of the gut microbiota and probiotics on CNS function have been shown to be dependent on vagus nerve activation.[18] How gut microorganisms achieve vagal activation is presently unknown and clearly unexplored vagus-independent pathways are involved as some CNS-microbiota-probiotic interactions are unaffected by vagotomy.[33]

PROBIOTICS AND AFFECTIVE DISORDERS

Both animal studies and human clinical data support a role for probiotics in the treatment of affective disorders. In rats subjected to maternal separation stress, treatment with *Lactobacillus* probiotics normalizes corticosteroid levels.[34] Abnormal stress responses in germ-free rodents are completely normalized by colonization with *Bifidobacterium infantis*.[15] A variety of different experiments in various strains of mice show that probiotics reduce anxiety-like and depressive-like behaviors. A combination of *L. helveticus* and *B. longum* restores gut barrier function and reverses postmyocardial infarction depression in a rat model.[35] The administration of *L. rhamnosus* to mice reduced anxiety- and depression-related activities, reduced GABA(Aα2) receptor mRNA expression in the prefrontal cortex and amygdala, but increased GABA(Aα2) in the hippocampus.[18] Human studies are limited. In a double-blind, placebo-controlled, randomized trial, healthy subjects received either a *L. helveticus* and *B. longum* probiotic formula or placebo.[36] Using standardized questionnaires to assess anxiety, depression, stress, and coping abilities, subjects receiving the probiotics had significantly less psychological disturbances than did controls. In another placebo-controlled study involving 132 subjects and probiotic-containing yogurt, people with depressed mood reported increased happiness and demonstrated improved cognition with probiotics compared to placebo.[37] Functional magnetic resonance imaging in healthy women administered *B. animalis, Streptococcus thermophilus, L. bulgaricus,* and *Lactococcus lactis* demonstrated that probiotics favorably alter functions in brain regions controlling central processing of emotion and sensation.[38] In patients with chronic fatigue syndrome, *L. casei* significantly decreases anxiety.[39] Probiotics that may provide favorable support in the setting of anxiety and depression have been termed psychobiotics.[29]

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CONCLUSION

Probiotics were first proposed as an adjunctive therapy for major depression in 2005. Since that time, data from animal and clinical studies are accumulating that support a role for probiotics in the management of affective disorders. Enough preclinical data have been assembled to support clinical trials. The profile of candidate psychobiotics includes beneficial behavioral effects in preclinical studies, production of neuroactive compounds, ability to decrease proinflammatory cytokines, and the capacity to reduce HPA axis activity. Probiotics with the promise to deliver psychobiotic activity include *B. infantis, B. longum, L. bulgaricus, L. casei, L. helveticus,* and *L. rhamnosus*. As with other probiotic applications, multistrain probiotic formulas may confer greater benefit than single strain preparations. Humans are indeed supraorganisms composed primarily of microorganisms that modulate our very emotions and moods.

TAKEAWAY POINTS

- The brain-gut axis is all communication between the brain and the gut.
- Brain-gut communication is modulated by the gut microbiota.
- The gut microbiota modulates the brain-gut axis through neurotransmitters and hormones.
- Stress alters gut microbiota populations.
- Probiotics can normalize stress responses in animals.
- Probiotics appear to have benefit in human depression, anxiety, and visceral pain perception.

CLINICAL APPLICATIONS
The Brain-Gut-Microbiota Axis

Here are some key clinical points to keep in mind when considering the brain-gut-microbiota axis and affective disorders:

- Patients with affective disorders should be evaluated for dysbiosis and increased gut permeability.
- Dysbiosis should be addressed using diet, probiotics, and prebiotics.
- *Bifidobacterium* and *Lactobacillus* probiotics show benefit in affective disorders in limited human trials.
- A multispecies *Bifidobacterium* and *Lactobacillus* probiotic formula is likely to have the greatest clinical benefit in affective disorders.

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? DID YOU KNOW?

- Gastric mucosa telomere length is shorter in people infected with *Helicobacter pylori* compared to uninfected subjects. Short telomeres are associated with aging.
- **Gastric mucosa telomere length also is shorter in people taking nonsteroidal anti-inflammatory drugs (NSAIDs) compared to nonusers.**
- The DNA in the heart is the most effective at repairing itself, while the brain DNA is unable to repair damage, according to studies by Nova Southeastern University researchers.
- **Oral glutathione supplementation exerts beneficial effects on skeletal muscles during exercise, resulting in reduced muscle fatigue.**
- Type 2 diabetic patients who participate in resistance exercise after eating improve both their glucose and triglyceride levels whereas exercising before eating only improves glucose concentrations.
- **Bone fractures in postmenopausal women are associated with severe symptomatic gum disease.**
- L-Carnitine supplementation at a dose of 1,000 mg/day can significantly reduce oxidative stress and increase antioxidant enzyme activity in patients with coronary artery disease.
- **Postmenopausal women with knee osteoarthritis who participated in high-impact jumping exercises experienced improvement in both the biochemical composition of cartilage and physical function.**
- A short nap can alleviate stress and enhance the immune systems of sleep-deprived men.
- **Curcumin can increase levels of serum adiponectin and decrease levels of leptin.**
- *Boswellia serrata* markedly reduced cerebral edema in patients irradiated for brain tumors.
- **Neck circumference may predict a person's risk of cardiovascular disease.**
- Sage (*Salvia officinalis*) can decrease the number of hot flashes menopausal women experience per day.
- **Curcumin extract at 1,890 mg/day for 12 weeks lowered levels of triglycerides and low-density lipoprotein (LDL) cholesterol and raised high-density lipoprotein cholesterol in patients with the metabolic syndrome.**
- Chemicals commonly found in sunscreen may interfere with male fertility, according to a new preliminary study by the National Institutes of Health.
- **Resveratrol stimulates the growth of neurons in the hippocampus of rat brains.**
- A high-sugar diet may exacerbate the toxic effects of Bisphenol A (BPA), according to a study in fruit flies.
- **Taking acetaminophen during pregnancy may promote the development of attention-deficit hyperactivity disorder (ADHD) in children.**