Probiotics, Stress Management, and Health

Did you know that the microbiota that inhabit your gut can influence your health and behavior? This paper explains the brain-gut axis and explores how the use of probiotics could help humans deal with the negative consequences of stress and live a happier and healthier life.

Eliot Zaeder
Ms. Russell

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In America, millions of people struggle each day with stress and many of them take prescription drugs to help manage their symptoms (Daily Life, 2017). While it is widely accepted within the scientific community that some stress is beneficial, it is also clear from research that chronic stress can cause physiological problems in the human body, including numerous diseases and disorders (Konturek et al., 2011). Interestingly, recent studies have honed in on the connection between stress, the gut microbiota, and the brain. This paper will examine the gut-brain axis, how stress affects the health of the gut, and how probiotics like *Lactobacillus* and *Bifidobacterium* can help mitigate stress. Introducing healthy bacteria into the human gut is a treatment for dealing with the physiological consequences of stress.

Traditionally, scientists thought that the brain alone controls the body's functions, and, therefore, our health (Collins, 2012). In the past decade, however, researchers have discovered a new and vital contributor to our health: the microbiome. Recent experimental data suggests that the human microbiome has a bidirectional interaction with the brain via what is called the "gut-brain axis" (Yarandi, 2016). This complex communication between the microbiota and the brain includes hormonal, immunological, and neuronal signaling, connecting the central, autonomic, and enteric nervous systems (Zhou et al., 2015). As scientists begin to understand the biological mechanisms that control communication along the gut-brain axis, this new information is providing exciting possibilities for disease prevention.

To get a sense of the immense scale of the microbiota, it is important to understand that the human gut contains ten times more microbiota cells than total cells in the human body (Johansson et al., 2011). More important than its size, the flora (or microbiota population) in the intestines have a vital mutualistic relationship with the human host. When given an energy rich and anaerobic environment, this immense colony of flora helps maintain an intestinal barrier and, in extension, the overall health within the body. The health of the microbiota is thought to have an important and direct connection to the health of humans, so an impaired microbiota population can lead to compromised health, and possibly disease (Zhou et al., 2015).

How, then, do the microbes in the gut influence the brain? The main avenue by which gut microbiota communicate with the brain is through the permeable intestinal walls of the gut (Yarandi, 2016). In order to understand how the intestines become more permeable, we must first define the functions of the intestinal barrier: a multi-layered membrane that regulates the absorption of nutrients and water from the intestinal lumen into the blood. The intestinal barrier also functions to prevent the entry of pathogenic microbiota into the gut (Kelly et al., 2015). A normal intestinal barrier is comprised of three layers: a protective mucus layer containing digestive enzymes, an epithelial layer made of tight junctions and endocrine cells, and lastly a "lamina propria" layer of immune cells. Scientists have discovered that gut microbiota are essential in protecting the epithelial tight junctions and preventing pathogenic bacteria from colonizing the gut epithelium (Yarandi, 2016). If this multi-layered lining is impaired, harmful

microorganisms can proliferate, produce toxins, and damage healthy flora. These harmful microbes and toxins can, in turn, negatively interact with the intestinal endocrine, immune, and nervous systems (Yarandi, 2016). Once the intestinal barrier is compromised and gut permeability increases, there are then three potential pathways in which gut flora can interact with the brain: via neurotransmitters, via the immune system, and via hormone release (Collins, 2012, Turna et al., 2015).

Examining each of these pathways can reveal the many intricate ways our microbiota can affect our psychical and mental health. To begin with, gut microbiota are capable of producing their own neurotransmitters, which directly influence the levels of discrete neurotransmitters in the body (Turna et al., 2015). Precursors of serotonin, dopamine, gamma-Aminobutyric acid (GABA), norepinephrine, and acetylcholine are all secreted by microorganisms in the intestine, which influence neural signaling between the gut and the brain (Turna et al., 2015). In fact, 95% of serotonin, a neurotransmitter crucial for regulating mental health, is manufactured almost exclusively in the gut (Camilleri, 2009). While healthy gut microbiota boost beneficial neurotransmitters, pathogenic microbiota in the gut increase the permeability of the intestinal barrier and lead to health problems by allowing harmful metabolites to enter the bloodstream and interfere with neurotransmitter production. All microbiota in the gut produce metabolites which include short chain fatty acids and lipopolysaccharides. Short chain fatty acids can travel via transporters through the bloodstream and pass through the blood-brain barrier and inhibit dopamine and serotonin uptake (Kelly et al., 2015). In addition, lipopolysaccharides can escape through the intestinal barrier and into the bloodstream where they can influence the brain directly, leading to potential negative health consequences (Yarandi, 2016).

Another significant way in which the gut microbiota communicates with the brain is via the immune system. Flora in the gut communicate directly with the immune system via receptors that are present on the immune cells in the epithelial layer. They then activate a signal transduction pathway that can modulate mitosis, apoptosis, and inflammatory responses. When harmful flora and receptors interact, they can give rise to cytokine molecules that are also involved in an inflammatory response (Turna et al., 2015). When gut permeability is increased, lipopolysaccharides can exit the gut and activate receptors on microglial cells, which release inflammatory cytokines in the central nervous system and lead to harmful neuroinflammatory problems. If this situation persists, it can lead to neurodegenerative diseases such as Alzheimer's and Parkinson's (Yarandi, 2016).

The gut microbiota are also able to connect with the brain via hormonal communication. Together, the hypothalamus, pituitary gland, and adrenal gland interact by releasing stress hormones such as cortisol, a long-term stress hormone, and norepinephrine, a short-term stress hormone. This hypothalamus-pituitary- adrenal axis, dealing with the stress response, causes an inflammatory response in the gut, leading to colonization of harmful bacteria (Konturek et al., 2011, Turna et al., 2015). The many pathways in which the gut microbiota can influence the brain highlights the complexity of the gut-brain axis.

There is great complexity in how stress affects the many functions that our microbiota perform in the body. Stress is defined as an “acute threat to homeostasis” it has been shown to adversely affect the human microbiome (Konturek et al., 2011). At a basic level, stress causes bodily responses that help maintain homeostasis and keep an organism alive. It turns out that the gastrointestinal tract is especially responsive to both external and internal stressors (Konturek et al., 2011). Furthermore, many studies show that strain on the gut caused by stress can increase

gut permeability and lead to an impaired intestinal barrier (Yarandi, 2016). Therefore, understanding the role of stress and its connection to the gut microbiome is crucial to developing new ways to promote human health.

The body first responds to stress by secreting the hormone corticotropin releasing factor, which influences inflammation and gut motility (Konturek et al., 2011). Corticotropin releasing factor also increases gut permeability, and pain perception. The pituitary gland responds to this hormone and releases adrenocorticotropic hormone, which in turn stimulates the adrenal glands to produce cortisol (Konturek et al., 2011). Cortisol, along with norepinephrine and epinephrine, prepare the body for a fight-or-flight response by raising blood-glucose levels, narrowing the arteries, causing an increased heart rate, and, most importantly, suppressing the immune system (Konturek et al., 2011). Corticotropin releasing factor receptors lie on the surface of white blood cells in the intestinal wall and directly convey the body's stress response to the intestines. Therefore, an increase in corticotropin releasing factor will activate an immune response that impairs the intestinal barrier (Konturek et al., 2011). Immune cells translate stress signals into the release of many neurotransmitters and proinflammatory cytokines, all of which negatively affect the gut microbiota. Proinflammatory cytokines, in proper amounts, make symptoms worse in order to initiate a stronger immune response from the body. However, an excess of proinflammatory cytokines can cause over-inflammatory reactions (Konturek et al., 2011). When administered to humans, inflammatory cytokines were found to induce depressive symptoms in 50% of treated patients (Turna et al., 2015). In addition, aging is characterized by increased inflammatory cytokines in the body (Kelly et al., 2015). Stress and the uptake of cytokines clearly affects the gut microbiome and human health.

While there are many negative consequences to a compromised microbiome, there are some promising and positive ways to use the power of the gut microbiota. Recent findings show that while the overall profile of the adult human microbiome stays relatively stable throughout your life, it can be changed through the use of antibiotics and probiotics (Turna et al., 2015). Antibiotics, medicines that inhibit specific microorganism growth, are designed to deplete harmful microbiota, but they can also deplete beneficial microbiota and inadvertently increase gut permeability (Turna et al., 2015). On the other hand, probiotics are designed to stimulate microorganism growth and show great promise as treatment to combat the negative effects of stress (Zhou et al., 2015). I believe that active use of probiotics in the diet can help maintain normal intestinal permeability, reduce inflammation, and encourage a gut environment where beneficial microbiota can aid in normal neurotransmitter production.

At the most basic level, the intestinal barrier acts as a shield which can be modified by gut microbiota or its metabolites (Kelly et al., 2015). By stimulating certain bacteria to grow in the gut, the intestinal barrier can be fortified and remain intact when exposed to stress triggers. In a recent study on probiotics, *Lactobacillus* and *Bifidobacterium* bacteria were placed in experimental models of colitis (an inflammation of the colon), and the results showed a clear reduction in gut permeability (Yarandi, 2016). The probiotics were able to upregulate transmembrane proteins that proved crucial to preserving tight junctions between epithelial cells. In the study, treatment with probiotics also enhanced mucus production, which protect the intestinal barrier (Yarandi, 2016). In another related study, many commercial strains of probiotics were tested on a human intestinal model (Jalonen et al., 2006). Each probiotic was observed for its adhesion to the gut and its ability to inhibit pathogen adhesion to intestinal mucus. By comparing the properties of many probiotics, the study also showed that

combinations of probiotic strains were more effective than single strains in inhibiting pathogen adhesion (Jalonen et al., 2006). Scientific evidence clearly suggests that the use of probiotics offers numerous health benefits and helps stimulate a healthy microbiota in humans.

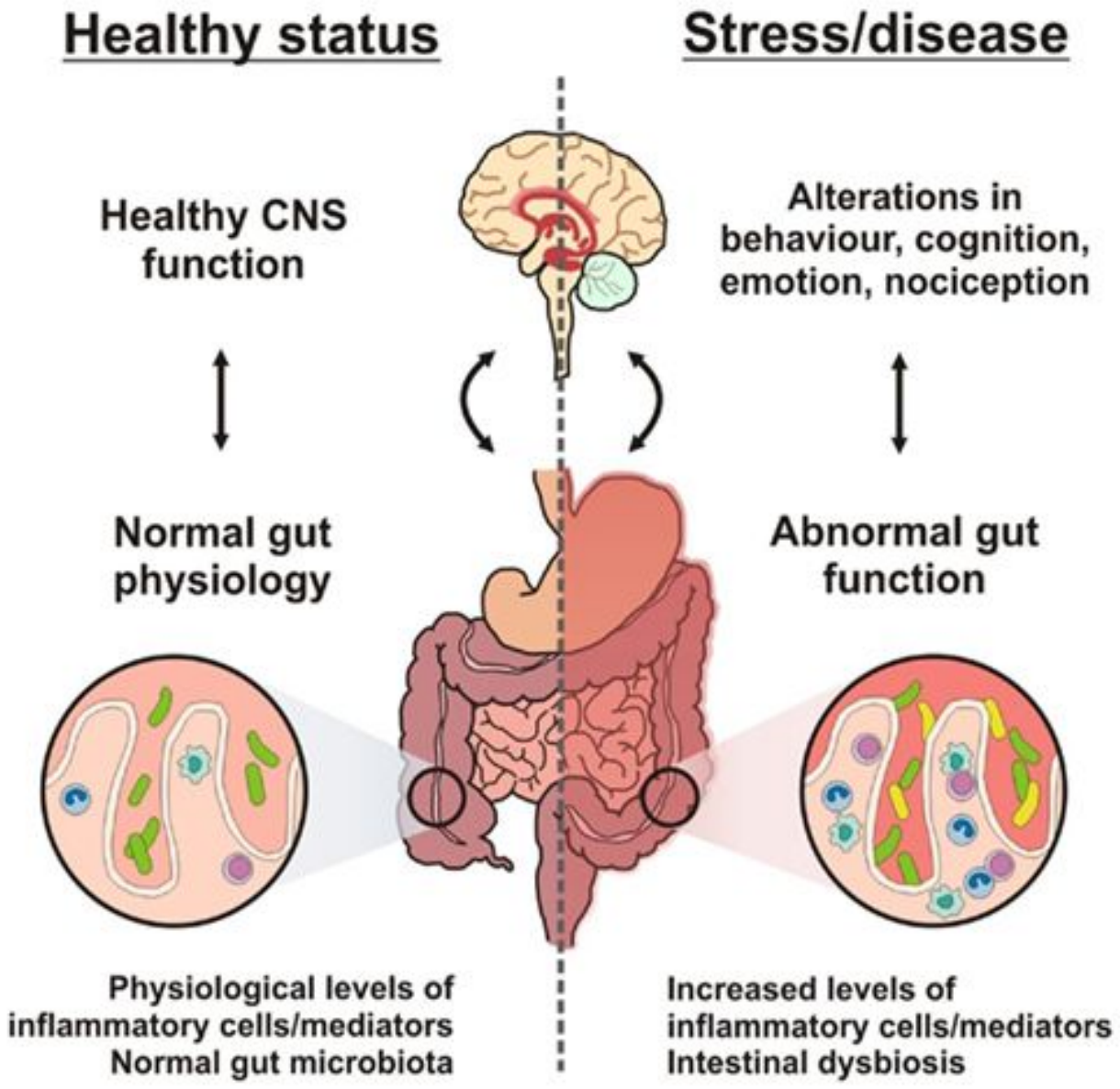
In addition to studying the beneficial effects of probiotics on the microbiota, recent trials have been testing the influence of probiotics on behavior and mood. One study involved a twenty-one day intake of probiotic milk that contained *Lactobacillus casei*, resulted in improved mood for healthy volunteers (Zhou et al., 2015). In another thirty day trial of consumption of probiotics containing *Lactobacillus helveticus* and *Bifidobacterium longum*, volunteers showed reduced anxiety, reduced depressive symptoms, and a reduced level of the stress hormone cortisol. The addition of probiotics to the diet was also shown to influence neural activity within emotional centers of the brain, confirming the direct connection between the gut and the brain (Zhou et al., 2015). These studies show clear evidence of a link between the use of probiotics and improved emotions. Understanding the connections between the human gut microbiome, probiotics, and the pathology of stress-related disorders may open up some exciting and promising treatment options (Kelly et al., 2015). The ability of probiotics to improve mood and reduce the detrimental effects of stress may help treat many disorders such as depression, obsessive compulsive disorder, anxiety, autism spectrum disorders, irritable bowel syndrome, and many more (Zhou et al., 2015). Surprisingly, the immense potential of probiotics on human health has not taken hold in modern medicine.

Even more promising for human health and medicine are findings that show that probiotics have the capability of increasing or decreasing the amount of neurotransmitters in the body. The addition of *Bifidobacterium infantis* to the diet was shown to increase levels of tryptophan, a precursor to serotonin, and consuming strains of *Lactobacilli* and *Bifidobacterium* produced the inhibitory neurotransmitter GABA (Turna et al., 2015). If *Lactobacilli* and *Bifidobacterium* produce GABA, then they indirectly act to inhibit neurons, hormones, and immune system inflammation. In a related study, mice under normal conditions showed increased neuronal excitability when introduced to stress. However, the inhibitory action of GABA was clear when these same mice were fed *Lactobacillus rhamnosus* and showed no such stress-induced excitability (Bravo et al., 2012). In another experiment involving mice ingesting *Lactobacillus rhamnosus*, it was discovered that the location of GABA receptors had changed. GABA B receptors had decreased in the amygdala and hippocampus (emotion centers of the brain), and had increased in cortical areas (hormonal center of the body) (Yarandi, 2016). These results affirm my strong belief that consuming *Lactobacilli* and *Bifidobacterium* can combat stress by leveraging the inhibitory action of GABA receptors. By lowering the excitability of the adrenal cortex and increasing the excitability of the emotion centers, these probiotics will reduce a hormonal response and increase an emotional response. I believe that strains of *Lactobacilli* and *Bifidobacterium* should be widely used in probiotics to help people combat stress-induced health issues.

Probiotic use could easily find its way into modern medicine. Much like the annual urine sample that we provide our doctors, a fecal sample could easily be taken too. With the use of inexpensive 16S rRNA tag sequencing, doctors can determine the composition of the gut microbiome. In addition, shotgun metagenomic sequencing allows clinicians to identify the functions of these microbes (Huse et al., 2012, Khanna et al., 2014). The Human Microbiome Project, which started in 2008, aims to sequence the entire microbiome of healthy human subjects to create a "core microbiome." By comparing a patient's microbiota profile to this "core

microbiome," doctors will be able to identify and prescribe a probiotic that can help their patient maintain a balanced microbiome. The addition of probiotics into the diet will help reincorporate missing bacteria back into the gut, promoting normal intestinal permeability, and better responses to stress (Huse et al., 2012). Because every human microbiome is different (due to hygiene, genetics, cultural background, etc.), many different strains of bacterial probiotics will have to be created and their effects studied before they are widely prescribed (Khanna et al., 2014). In the future, the use of probiotic therapy to manipulate the microbiome shows great promise in treating a variety of human health issues.

Fig. 1 Effects of health on gut physiology and CNS function



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