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Microbes and the Mind

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Introduction

In a busy world, striking a balance between daily life and maintaining good health is a challenge. The media and other information sources are continually bombarding us with health advice, and it is difficult to sort out fact from fiction. One of the leading newsworthy topics at the moment is our microbiota and its role in health. Within this broad topic, an interesting finding is the link between bacteria in the gastrointestinal (GI) tract and mental health. Scientists have established a link between gut bacteria and anxiety-like behaviors in animal models (Heijtz *et al.*, 2011; Neufeld *et al.*, 2011a; 2011b; Clarke *et al.*, 2013), and with emotional brain regions in healthy people (Tillisch *et al.*, 2013). This emerging area of research has led scientists and the public to start to take notice of microbes and the mind.

The word microbiota refers to all of the microorganisms that inhabit our gastrointestinal tract and other bodily surfaces; whereas the word microbiome refers to all the genetic material associated with such microorganisms. Much of the ongoing research is looking at gut microbiota and its role in the function of the gut-brain axis. Here, we will review some of the recent findings related to how the microbiota influences anxiety-like behavior and provide some insight into the possible pathways and mechanisms that connect the microbiota to the brain.

Gut microbiota and effects on behavior

Attention to the gut-brain axis and a potential role for microbiota in stress-related behaviors was ignited by a report showing that germ-free mice had an exaggerated stress response (Sudo *et al.*, 2004). Germ-free mice are raised in a sterile/gnotobiotic environment and have no commensal bacteria. As gut microbiota are necessary for the development of the immune system,

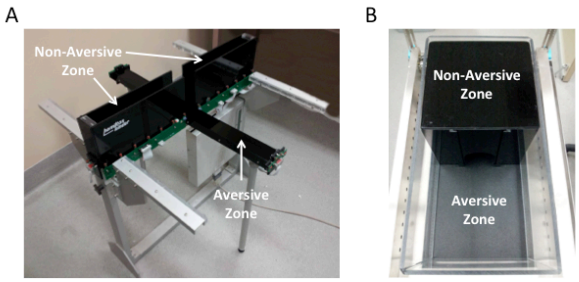

Figure 1 ~ Behavioral neuroscience uses the elevated plus maze (A) and the light/dark test (B) to measure anxiety-like behavior. Each apparatus has a non-aversive (dark, closed) area and an aversive (well lit, open) area. Anxiety-like behavior is associated with time spent in the non-aversive zone, and reduced anxiety-like behavior is suggested when the mice spend more time in the aversive zones.

germ-free mice have an undeveloped immune system (Cebra, 1999). Sudo and colleagues (2004) showed that in response to immobilization stress, germ-free mice had exaggerated levels of stress hormones, corticotrophic hormone and adrenocorticotrophic hormone, in their plasma compared to conventionally housed mice (Sudo *et al.*, 2004). In addition, germ-free mice showed altered levels of key stress neurochemicals in brain tissue compared to conventionally housed mice (Sudo *et al.*, 2004). Several studies since this report have examined anxiety-like behavior in germ-free mice using standard behavioral tools (Heijtz *et al.*, 2011; Neufeld *et al.*, 2011a; 2011b; Clarke *et al.*, 2013).

Using the elevated plus maze (see Figure 1), the gold standard for testing anxiety-like behavior in neuroscience, Neufeld *et al.* (2011) showed that germ-free mice spent more time in the aversive open arm area of the elevated plus maze than conventionally housed mice, and that the number of times they entered the open arms of the maze was higher, demonstrating a reduced level of anxiety-like behavior in germ-free mice (Neufeld *et al.*, 2011b).

This finding was replicated by Heijtz *et al.* (2011), also using the elevated plus maze, and by Clarke *et al.* (2013), who showed reduced anxiety-like behavior in germ-free mice using the light/dark test, an approach/avoidance behavioral test used to test anxiety-like behavior in mice. Together these findings revealed a reduced anxiety-related phenotype in mice lacking microbiota. This is a little surprising as these mice show an increased response to stressors, however, this may suggest that the circulating stress hormones are not critical to the normal state of anxiety-related behavior.

The link between the immune system and behavior is long-standing and since the gut microbiota is essential for immune system development, it is thought that it is an important mediator between inflammation and anxiety-like behavior (Foster and McVey Neufeld, 2013). Studies that manipulate gut microbiota in rodents alter the immune status of the animal and, in parallel, alter the behavioral phenotype observed (Figure 2).

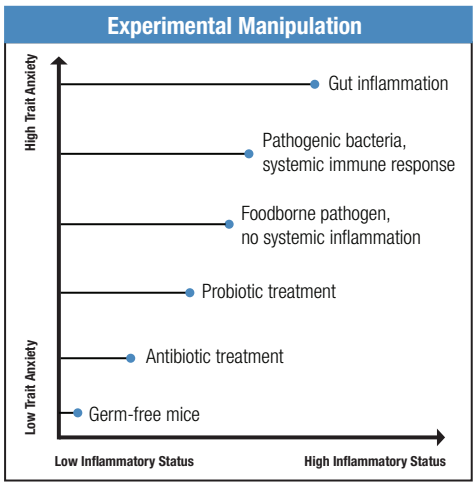

Figure 2 ~ Research suggests that microbiota may be an important mediator between inflammation and anxiety-like behavior. This schematic summarizes several studies where experimental manipulations that alter the microbiota profile also impact the inflammatory state and anxiety-like behavior. Across studies, low levels of inflammation are associated with low trait anxiety and increased inflammation is associated with increased anxiety-like behavior (Foster and McVey Neufeld, 2013).

Exposure to broad-spectrum antibiotics in drinking water has been shown to alter the profile of gut microbiota, reduce intestinal permeability of the GI tract, and thereby decrease the inflammatory state. Administration of a mixture of antibiotics including neomycin (5 mg/ml) and bacitracin (5 mg/ml), with an antifungal agent, reduced the anxiety-like behavior in mice (Bercik *et al.*, 2011a). Antibiotic treatment in germ-free mice did not alter the behavioral phenotype supporting the conclusion that the behavioral changes were mediated by the microbiota (Bercik *et al.*, 2011a). In addition to antibiotic treatment, probiotic administration to healthy rodents can alter behavior. Probiotics are microorganisms that when consumed confer a health benefit to the host (FAO/WHO expert, 2001).

Administration of *Lactobacillus rhamnosus* (JB1) to healthy adult male mice reduced both anxiety-like and depressive-like behaviors following 28 days of probiotic treatment (Bravo *et al.*, 2011). In a different study, administration of a mixture of probiotics for 14 days, including *Lactobacillus helveticus* and *Bifidobacterium longum*, reduced anxiety-like behavior in rats, determined using the defensive marble burying test (Messaoudi *et al.*, 2011a). The same probiotic mixture reduced measures of psychological stress following 30 days administration in healthy volunteers, suggesting that probiotics may hold promise for clinical treatment in mood and anxiety disorders (Messaoudi *et al.*, 2011a). While neither of these studies examined the inflammatory state following probiotic administration, other studies have demonstrated reduced inflammation following probiotic treatment (Arseneault-Bréard *et al.*, 2012; Luo *et al.*, 2014). Overall, the data from germ-free mice, antibiotic treatment, and probiotic administration to healthy individuals suggests that alterations in gut microbiota that reduce the inflammatory state also reduce stress-related behaviors.

Bacterial infection and increased inflammation is associated with increased anxiety-like behaviors; further, the magnitude of change observed in the behavior corresponds to the magnitude of the inflammatory change. For example, oral administration of a sub-pathogenic dose of bacteria such as *Citrobacter rodentium* and *Campylobacter jejuni* increased anxiety-like behavior in mice, although this effect was short-acting (eight hours) and was not evident at later times (Lyte *et al.*, 1998; Goehler *et al.*, 2005; Lyte *et al.*, 2006). These behavioral changes were accompanied by activation of neurons in central stress circuits, however, there was no systemic immune response to the low dose exposure to these foodborne pathogens (Lyte *et al.*, 1998; 2006; Goehler *et al.*, 2008). This work demonstrates that a local GI inflammatory stimulus can communicate with neurons in the central nervous system and influence behavior. In contrast, activation of an innate immune response following peripheral infection in rodents increases anxiety-like behavior and also impacts other behaviors including depressive-like behavior, and often learning and memory. Evidence that alterations in microbiota mediate the link between peripheral infection and anxiety-like behavior is emerging. For example, infection with the non-invasive nematode parasite *Trichuris muris* in mice resulted in gastrointestinal inflammation and increased anxiety-like behavior (Bercik *et al.*, 2010). A role for microbiota in mediating this response was evident as probiotic treatment with *B. longum* normalized behavior in these mice (Bercik *et al.*, 2010).

As evidence accumulates for a role of microbiota in brain function and behavior, a key question is whether consumption of probiotics influences behavior. Several studies in the past five years have examined the impact of probiotic administration on behavior. Evidence of a role for gut bacteria in normal body homeostasis is provided by studies that show a reduction in anxiety-like and depressive-like behaviors following probiotic administration to healthy rats and mice (Bravo *et al.*, 2011; Messaoudi *et al.*, 2011a; Matthews and Jenks, 2013).

Importantly, related work in healthy adults provides good evidence that the animal studies may translate to people. Two key studies have been reported to date. In the first, Messaoudi and colleagues (2011) conducted a double-blind, placebo-controlled, randomized study where healthy volunteers received a mixture of *L. helveticus* and *B. longum* for 30 days. Individuals were assessed using several clinical questionnaires including the Hopkins Symptom Checklist, the Hospital Anxiety and Depression Scale, the Perceived Stress Scale, and the Coping Checklist. The results showed that administration of the probiotic mixture influenced the psychological state of healthy volunteers, and specifically individuals showed reduced general signs of anxiety and depression. Interestingly, these psychological effects were accompanied with a decrease in stress hormone, cortisol, levels over time (Messaoudi *et al*., 2011a). In the second study, Tillisch and colleagues (2013) provided a link between probiotics and brain activity. Healthy individuals consumed a fermented milk product with or without probiotics for 28 days. The probiotic mixture included *Bifidobacterium animalis* subsp. *lactis*, *Streptococcus thermophiles*, *Lactobacillus bulgaricus*, and *Lactococcus lactis* subsp. *lactis*. Functional magnetic resonance imaging (fMRI) demonstrated that individuals that consumed the probiotic mixture had altered brain activity in resting state and a reduced response to an emotional-recognition task (Tillisch *et al*., 2013). Together these studies provide good evidence that microbiota-brain signaling is important to normal homeostatic processes and everyday brain function.

As research continues it is more evident that probiotic administration may have therapeutic potential as several animal studies show normalization or improvements in behavior deficits in animal models of disease. It should be noted that a limited number of probiotics have been tested to date; however, some have been shown across studies to have beneficial effects, particularly in the area of anxiety and depression. Here we review a selection of key studies in this area. *B. longum* has been shown to normalize inflammation-induced anxiety-like behavior following *Trichuris muris* infection (Bercik *et al*., 2010) and in a dextran sulfate sodium (DSS)-colitis model (Bercik *et al*., 2011b). *Bifidobacterium infantis* has been shown to normalize stress-induced increases in depressive-like behavior induced by early life maternal separation, suggesting a more specific role for microbiota-gut-brain communication in response to early life stressors (Desbonnet *et al*., 2010). *L. reuteri* administration has been shown to reduce stress-related increases in anxiety-like behavior (Mackos *et al*., 2013). *L. helveticus* administration has been shown to prevent diet-induced increases in anxiety-like behavior in wild type mice but not in interleukin 10 (IL10) knock-out mice (Ohland *et al*., 2013). *L. helveticus* also prevented hyperammonemia-induced anxiety-like behavior in rats and showed a beneficial effect to correct learning and memory retention deficits (Luo *et al*., 2014) suggesting that immune signaling pathways may play a role in the probiotic effect. Probiotic mixtures have also been tested, for example, *L. helveticus* combined with *B. longum* was shown to prevent or attenuate myocardial infarction-induced anxiety-like behavior, deficits in social interaction, and depressive-like behavior in rats (Arseneault-Bréard *et al*., 2012; Gilbert *et al*., 2013). Overall these studies provide substantial evidence that gut bacteria can effectively modulate behavior.

Potential mechanisms by which microbes influence behavior

There are several mechanisms by which microbiota may modulate the gut-brain axis and influence behavior including; immune signaling, neural pathways, altering neurotransmitter levels and gene expression in the CNS, and changes in intestinal permeability, among others (Figure 3). As noted above, a strong association exists between inflammatory state and anxiety-like behavior. It is of interest to understand how changes in gut inflammation, peripheral blood immune markers, and changes in brain immune signaling systems, influence behavior; however, the related literature is too broad in scope to be reviewed here. Key papers and their findings related to immune signaling and inflammation are integrated into the discussion below.

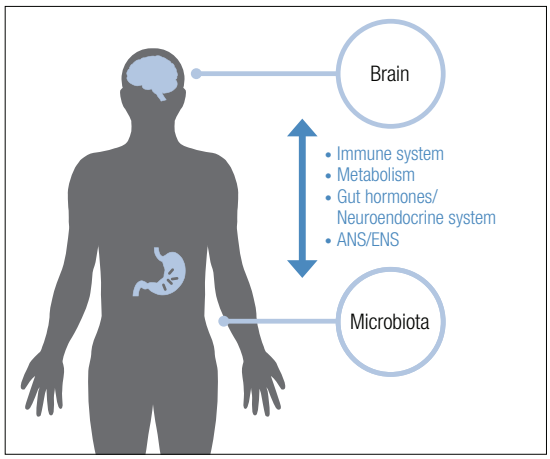

Figure 3 ~ Schematic of the gut-brain axis. Microbiota-brain communication is bidirectional and continual. Several pathways influence the communication between gut microbiota and the brain including the immune system, metabolism, gut hormones, the neuroendocrine system, the autonomic nervous system (ANS), and the enteric nervous system (ENS).

Intestinal permeability is an important factor to consider when considering pathways connecting microbiota to the brain. Increased intestinal permeability is commonly referred to as 'leaky gut' and it is common to find news articles linking a leaky gut to depression. A recent news article (Rodriguez, 2013) refers to a clinical study conducted by Maes and colleagues (2012) that showed that 35 percent of depressed patients had evidence of immune-reactivity to commensal bacteria in their blood (Maes *et al.,* 2012). The presence of this immune response was associated with GI symptoms in this subset of patients (Maes *et al.,* 2012). In the research area linking stress and gut microbiota, reviewed recently by Dinan and Cryan (Dinan and Cryan, 2012), several studies have examined changes in microbiota, intestinal permeability, and stress reactivity (Gareau *et al*., 2008), however, only a few reports to date have linked these changes to behavior.

For example, myocardial infarction induces increased anxiety-like behavior, but also leads to increased intestinal permeability measured by fluorescein isothiocyanate–dextran (FITC) serum recovery four hours following oral gavage, in rats (Arseneault-Bréard *et al.*, 2012). Probiotics, *L. helveticus* and *B. longum*, reversed the myocardial infarction-induced changes in intestinal permeability in parallel with normalization of anxiety-like behavior (Arseneault-Bréard *et al.*, 2012).

Neural pathways, including the enteric nervous system and the autonomous nervous system, are central to the bidirectional communication of the gut-brain axis. Several reports have used subdiaphragmatic vagotomy to block vagal nerve communication to the brain and their results suggest a role for the vagus nerve in mediating gut microbiota-brain communication. For example, *L. rhamnosus* administration-related alterations in anxiety- and depressive-like behaviors were blocked in vagotomized mice (Bravo *et al.*, 2011). In addition, the ability of *B. longum* to reverse DSS-colitis and induce anxiety-like behavior was demonstrated to be vagally mediated. In this example it is important to note that *B. longum* administration did not prevent the GI inflammatory response to DSS, as measured by myeloperoxidase activity and histological evidence of inflammation in the colon (Bercik *et al.*, 2011b), although circulating immune markers and brain immune molecules were not examined. Similar to this result, Mackos and colleagues (2013) showed that administration of the probiotic mixture, *Lactobacillus acidophilus*, *B. lactis*, and *Lactobacillus fermentum* normalized anxiety-like behavior, but did not reduce gut inflammation caused by stress-enhanced *C. rodentium*-induced infectious colitis (Mackos *et al.*, 2013). In contrast to the above probiotic administration studies, antibiotic-induced reduction in anxiety-like behavior was not effected by vagotomy (Bercik *et al.*, 2011a). Antibiotic treatment in this study resulted in a complex change in the profile of gut microbiota including a significant increase in the phyla Firmicutes and Actinobacteria, and a decrease in Proteobacteria and Bacteriodetes. The authors suggest that the altered behavior in this model related to changes in substances produced by this modified profile of gut bacteria that may directly or indirectly act on brain systems (Bercik *et al.*, 2011a).

Several experimental manipulations of microbiota have resulted in changes in gene and protein expression levels in the CNS, and alterations in neurotransmitter levels. In germ-free mice, neuroplasticity gene, brain-derived neurotrophic factor (BDNF), mRNA and protein levels are altered in hippocampal and cortical regions (Sudo *et al.*, 2004; Heijtz *et al.*, 2011; Neufeld *et al.*, 2011b; Clarke *et al.*, 2013). Although there is inconsistency in the nature of alterations of BDNF levels related to sex and strain in germ-free mice, these findings clearly link microbiota to neuroplasticity-related CNS systems. In support of this connection, antibiotic treatment in mice also alters BDNF protein levels in key brain regions (amygdala and hippocampus) implicated in anxiety- and depressive-like behaviors (Bercik *et al.*, 2011a).

Higher expression of synaptic-related proteins was reported in germ-free mice compared to conventionally housed mice (Heijtz *et al.*, 2011) suggesting long-term adaptive change in brain circuitry may contribute to changes in behavior observed in germ-free mice.

In addition to neuroplasticity and synaptic systems, the microbiota has been reported to influence neurotransmitter levels in brain tissue. In germ-free mice, monoamine neurotransmitters including dopamine and serotonin levels are altered (Heijtz *et al.*, 2011; Clarke *et al.*, 2013) and associated changes in serotonin and dopamine receptors have been reported (Heijtz *et al.*, 2011; Neufeld *et al.*, 2011b; Clarke *et al.*, 2013). Also to note, probiotic administration of *L. rhamnosus* in mice altered inhibitory neurotransmitter receptor (GABA-Aα1, GABA-Aα2) mRNA levels in several stress-related brain regions (Bravo *et al.*, 2011). Peripheral changes in tryptophan metabolism may underlie some of the central changes in monoamine systems as germ-free mice showed increased plasma tryptophan and reduced kynurenine/tryptophan ratios (Clarke *et al.*, 2013). A similar profile was observed following two weeks of *Bifidobacterium infantis* treatment in healthy rats without a behavioral effect (Desbonnet *et al.*, 2009), however, in a different study, *B. infantis* administration was not able to reverse the maternal separation-induced changes in tryptophan metabolism (Desbonnet *et al.*, 2010) suggesting the importance of microbiota-brain interactions to early life brain development.

Future prospects

Research to date has provided clear evidence that bacteria influence brain function and behavior. Moving forward, more clinical work directly examining the microbiota-gut-brain axis in individuals with depression and anxiety disorders is needed. Approaches that include comprehensive analysis of immune markers, gut function and brain activity, in both healthy individuals and those with mood and anxiety disorders, will pave the way for trials to test the therapeutic potential of probiotics in mental health. Extending the research related to probiotics to include a broader spectrum of commensal bacteria will also aid our understanding of the specificity of probiotics in improving anxiety and depressive-related symptoms.

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