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Review

REVIEW

Gut Microbiota and Brain Function: An Evolving Field in Neuroscience

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Abstract

There is a growing appreciation of the importance of gut microbiota to health and disease. This has been driven by advances in sequencing technology and recent findings demonstrating the important role of microbiota in common health disorders such as obesity. Moreover, the potential role of gut microbiota in influencing brain function, behavior, and mental health has attracted the attention of neuroscientists and psychiatrists. At the 29th International College of Neuropsychopharmacology (CINP) World Congress held in Vancouver, Canada, in June 2014, a group of experts presented the symposium, "Gut microbiota and brain function: Relevance to psychiatric disorders" to review the latest findings in how gut microbiota may play a role in brain function, behavior, and disease. The symposium covered a broad range of topics, including gut microbiota and neuroendocrine function, the influence of gut microbiota on behavior, probiotics as regulators of brain and behavior, and imaging the gut-brain axis in humans. This report provides an overview of these presentations.

Keywords: Behavior, brain imaging, immune, neuroendocrine, MRI, probiotic

Microbiota and Behavior

The role of the microbiome in the determination of behavior and cognition is increasingly being recognized (Cryan and Dinan, 2012; Collins et al., 2013; Foster and McVey Neufeld, 2013; Lyte, 2013). In fact, the development of the brain itself in the growing infant has been shown to be influenced by the microbiome (Douglas-Escobar et al., 2013). As such, the communication of gut microbiota with the brain, through what is referred to as the microbiota-gut-brain axis, represents a new biological axis by which novel diet-based therapies can be designed to influence brain function and behavior. Early studies in animals first demonstrated that the introduction of a single, unique bacterium in the gut resulted in the development of anxiety-like behavior in mice, with concomitant activation of neuronal regions in the brain that were dependent on information received from the gut via the vagus nerve (Goehler et al., 2005). Later studies showed that the transplantation of the fecal microbiome from one mouse strain displaying a phenotypic set of behaviors to another strain resulted in the recipient strain exhibiting the behavioral phenotype of the donor (Bercik et al., 2011a; Collins et al., 2013). Ongoing research continues to demonstrate in humans that the composition of the microbiota has a dramatic influence on the behavior of the individual. For example, the composition of the mucosal microbiota of cirrhotic patients was linked to poor cognition (Bajaj et al., 2012).

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Much of our understanding related to how microbiota may influence behavior comes from animal studies that manipulate the composition and diversity of gut microbiota. The germ-free (GF) mouse has been a useful animal model to help determine the domains of behavior that are influenced by microbiota. The GF mouse model was established in 1957, where GF mice are raised in sterile/gnotobiotic environments and have no commensal bacteria (Gustafsson et al., 1957; Gustafsson, 1959). Both the mucosal and the systemic immune systems of GF mice are immature, with reduced numbers of B lymphocytes and T lymphoctyes (Macpherson and Harris, 2004). A landmark study showed that GF mice have exaggerated stress-reactivity in response to restraint stress, revealed by increased plasma corticosterone and plasma adrenocorticotrophic hormone levels compared to specific pathogen-free (SPF) mice (Sudo et al., 2004). This publication was really the stimulus for neuroscientists to consider the GF mouse model (Sudo et al., 2004). The question arose as to whether or not GF mice would show an altered behavioral phenotype. Several research groups have examined behavior in germ-free mice; these studies are summarized in Table 1. Across these studies, some common findings have emerged. First of all, GF mice show reduced anxiety-like behavior, compared to conventionally-housed mice, in the elevated plus maze (EPM) and light/dark test (Heijtz et al., 2011; Neufeld et al., 2011b; Clarke et al., 2013). Second of all, reconstitution of GF mice with strain-matched microbiota early in life is able to normalize many of the behaviors (Heijtz et al., 2011; Clarke et al., 2013), whereas reconstitution of GF mice in adulthood was not able to change the reduced trait anxiety–like phenotype observed in the EPM (Neufeld et al., 2011a). Interestingly, one can argue that the behavioral phenotype is linked directly to the microbiota, as the transfer of SPF Balb/C microbiota to GF Swiss Webster (SW) mice reduced exploratory behavior compared to normal SW mice, while transfer of SPF SW microbiota to GF Balb/C mice increased exploratory behavior compared to normal Balb/C mice (Bercik et al., 2011a). In stress-sensitive F344 rats, GF rats showed reduced social interaction, reduced center entries in the open field (OF), and increased time spent in the corners of the OF (Crumeyrolle-Arias et al., 2014). These observations are opposite the exploratory and anxiety-like differences mentioned above in several non–stress sensitive strains of mice; however, these observations parallel social behavior deficits that have been reported in GF SW mice (Desbonnet et al., 2013). Together, the above studies identify both exploratory and anxiety-like behaviors and social behavior as domains that are influenced by microbiota. The suggestion that strains modulate the influence of microbiota is important to consider and was addressed in a recent paper using stress-sensitive Balb/C mice. Researchers compared GF Balb/C mice to the offspring of conventionalized GF Balb/C mice (EX-GF) and showed less anxiety-like behavior in EX-GF mice in both the OF and in the marble burying test (Nishino et al., 2013). Monoassociation with *Clostridium coccoides* also reduced anxiety-like behavior, whereas monoassociation with *Bifido infantis* showed reduced activity in the OF and no changes in anxiety-like behavior compared to GF mice (Nishino et al., 2013). Understanding which microbiota specifically influence behavior is a central theme of ongoing research in this area.

Probiotic Studies in Animals

Several groups have examined the effect of probiotic administration on behavior. Initial reports in rats showed no effect of probiotic administration to healthy rats. First, administration of *Lactobacillus salivarius, B. infantis, or B. breve* to healthy Sprague-Dawley or Wistar rats had no effect on open field behavior (McKernan et al., 2010). Second, administration of *B. infantis* to healthy Sprague-Dawley rats showed no effect on depressive-like behavior in the forced swim test (FST; Desbonnet et al., 2008): however, 45 days of treatment with *B. infantis* in rats exposed to early-life maternal separation normalized stress-induced depressive-like behavior in the FST (Desbonnet et al., 2010). Similarly, probiotic treatment has been shown to be beneficial in animal models of infection and colitis (Bercik et al., 2010, 2011b). Specifically, administration of *L. rhamnosous* for 10 days normalized anxiety-like behavior induced by the parasite *Trichuris muris* (Bercik et al., 2011b) and administration of *B. longum* for 14 days normalized anxiety-like behavior induced by dextran sodium sulphate colitis (Bercik et al., 2011b). Interestingly, a few studies have reported a change in behavior when probiotics are administered to healthy rodents. For example, 28-day administration of *L.rhamnosous* to Balb/C mice resulted in reduced anxiety-like behavior in the EPM and reduced depressive-like behavior in the FST (Bravo et al., 2011). It has also been shown that *B. Breve* and *B. Longum* both significantly reduced anxiety-related behaviors, albeit with different profiles (Savignac et al., 2014), and the latter strain, but not former, enhanced cognitive function in healthy Balb/C mice (Savignac et al., 2015). Also, 14-day administration of the combination of *L. helveticus* and *B. longum* reduced anxiety-like behavior in the defensive marble burying test in Wistar rats (Messaoudi et al., 2011a). Interestingly, administration of this combination of probiotics to healthy human subjects showed a beneficial effect on anxiety and depression measures (Messaoudi et al., 2011b). Other combinations of probiotics have been shown to reduce a sad mood triggered by a psychological stimulus (Steenbergen et al., 2015) and to reduce depression anxiety and stress scales whilst modulating the hypothalamic pituitary adrenal (HPA) axis in petrochemical workers (Mohammadi et al., 2015).

Microbiota, Immune Signaling, and the Brain

While several gut-brain pathways are suggested to play a role in microbiota-to-brain signaling (Cryan and Dinan, 2012; Foster and McVey Neufeld, 2013), this CINP symposium presented key findings related to the role of immune signaling in behavior. Researchers in psychiatry and behavioral neuroscience are increasingly recognizing the importance of the adaptive immune system in behavior. Recombinase-activating gene-1 (RAG-1) is a component of the adaptive immune recombination system (Chun et al., 1991). Deletion of RAG-1 results in the ability of lymphocytes to execute VDJ recombination, a mechanism of genetic recombination that rearranges variable (V), joining (J), and diversity (D) gene segments to create diversity in the variable chain of the T cell receptor. This deletion generates mice that lack mature T and B cells, thus silencing the adaptive immune system (Mombaerts et al., 1992). *RAG1-/-* mice (Cushman et al., 2003) show reduced anxiety-like behavior. Mice lacking both β-2 microglobulin and transporters associated with the antigen processing genes ($\beta 2M-/-TAP-/-$), resulting in the loss of functional class I major histocompatability complex (MHC) molecules and depleted CD8 T cells (Sankar et al., 2012), show no differences in time spent in the open arm of the EPM; however, they show increased risk assessment behaviors (Sankar et al., 2012). Mice lacking T cell receptor β and δ chains ($TCR\beta-/-\delta-/-$) and deficient of T cells showed reduced anxiety-like behavior in the EPM, light/dark test, and OF, whereas these behavioral differences are not observed in B cell deficient mice (Rilett et al., 2015). In

Table 1. Behavioral outcomes in germ-free mice

	Behavioral Test	Sex/Strain/ Species	Outcome	Ref
GF, Conventionalized (8 w) GF mice	EPM	F SW mice	• GF mice spent more time in open arms, showed increased # of open arm entries, no activity difference • Conventionalization of GF mice at 8 w of age did not reverse the behavioral phenotype	(Neufeld et al., 2011a, 2011b)
GF, SPF Conventionalized (dams prior to mating)	EPM Light/Dark Test OF	M NMRI	• GF mice spent more time in open arms of EPM and more time in light chamber of L/D test • GF mice showed increase motor activity and rearing in OF • Offspring of conventionalized dams spent more time in light chamber comparable to GF mice, however other behaviors normalized	(Heijtz et al., 2011)
GF, SPF GF SW colonized with Balb/C or SW SPF microbiota GF Balb/C colonized with Balb/C or SW SPF microbiota	Light/Dark Test; step-down	M Balb/C and SW mice	• SPF Balb/C mice exposed to 7 days of antibiotic cocktail spent more time in the light chamber of the light/dark test and showed increased transitions; in addition, the stepped down faster from elevated platform • Two week washout following antibiotic treatment reversed the Behavioral effects and altered microbiota profile • Antibiotic treatment of GF mice did not alter behavior • Vagotomy did not alter antibiotic effects on behavior • GF SW mice colonized with SPF Balb/C microbiota showed reduced exploratory behavior than GF SW mice colonized with SPF Swiss Webster microbiota • GF Balb/C mice colonized with SPF SW microbiota showed more exploratory behavior than GF Balb/C mice colonized with SPF Balb/C microbiota	(Bercik et al., 2011a)
GF, Conventional, Conventionalized (P21) GF mice (GFC)	Light/Dark Test	M and F SW mice	• GF mice transitioned more between the light and dark chamber in the light/dark test • Conventionalization of GF mice at P21 normalized behavior in the light/dark test	(Clarke et al., 2013)
GF Conventionalized (P21) GF mice (GFC)	3 chamber social behavior; social transmission of food preference	M and F SW mice	• GF mice show reduced sociability which normalized in GFC mice • GF mice did not show normal social preference of novel mouse which did not normalize in GFC mice • GF mice showed reduced social investigation and increase self-grooming during the social transmission of food preference test	(Desbonnet et al., 2013)
Expt 1 – GF, GF 24 h in SPF conditions Expt 2 – GF, EX-GF (offspring of conventionalized GF mice), Bi – GF monoassociated with Bifido infantis, Bc – GF monoassoicated with Clostridium coccoides	OF; marble burying test	M Balb/C mice	• Expt 1 - GF mice retested after 24h exposure to normal housing conditions showed reduced number of marbles buried and reduced time spent in the periphery of the OF; no differences seen in GF mice retested in GF conditions • Expt 2 – reduced number of marbles buried at 10 and 16 w of age and reduced time spent in the periphery of the OF in EX-GF mice compared to GF mice at 7, 10 and 16 w of age, also reduced distance travelled in OF across time points • Expt 2 – Bc mice showed reduced time spent in the periphery of the OF at 7 and 10 w of age and reduced number of marbles buried across time points • Expt 2 - Bi mice showed reduced activity (distance travelled) in the OF across time points	(Nishino et al., 2013)
GF, SPF	Social interaction; OF	M F344 stress-sensitive rats	• GF rats showed less sniffing behavior during the first 2 min of the social interaction test • GF rats showed reduced center entries, increased latency to first move, and increased time spent in the corners of the open field (6 min test)	(Crumeyrolle-Arias et al., 2014)

EPM, Elevated Plus Maze; EX-GF, the offspring of conventionalized GF Balb/C mice; F, female; GF, germ-free; M, male; OF, open field; SPF, specific pathogen free; SW, Swiss Webster

the study with $\beta 2M-/-TAP-/-$ mice we observed a loss of sexual dimorphism in activity, exploratory, and anxiety-like behaviors compared to B6 mice (Sankar et al., 2012). This was also observed in $TCR\beta-/-\ \delta-/-$ mice (Rilett et al., 2015). Considering the evidence of sexual dimorphisms in immune functioning (Weinstein et al., 1984; Da Silva, 1999; De Leon-Nava et al., 2009), it is seems reasonable and necessary to further examine a role for immune phenotype in sex differences in behavior.

Microbiota Produce Neurochemicals that Affect the Brain

In many of the studies that have addressed mechanisms by which microbes can influence behavior, the conclusions are that such mechanisms involve the immune system to some degree, as noted in the above section. This is not surprising given that such studies often involve the administration of a microorganism in a manner that nearly guarantees an immune system response. However, mechanisms by which microbiota-gut-brain communication can occur that are non-immune mediated are becoming an area of growing research interest (Lyte and Cryan, 2014a).

The ability of bacteria to produce and recognize neurochemicals (Lyte, 2013) provides a mechanistic basis with which to examine the ability of the microbiota to influence the microbiome-gut-brain axis. The recognition that prokaryotic, as well as eukaryotic, microorganisms produce, as well as possess, receptors for a wide range of neuroendocrine hormones has in fact been known for decades (for reviews see Lenard, 1992, and Roshchina, 2010). The range of neurohormones that are found in microorganisms is extremely diverse, ranging from somatostatin to acetylcholine to progesterone. Critically, microorganisms which inhabit the gastrointestinal tract are capable of producing neurochemicals that can bind to host receptors (intra- and extra-intestinal) in sufficient quantities to effect neurophysiological changes in the host. Asano et al. (2012) established that the microbiota is capable of the *in situ* production of the biologically active neuroendocrine hormones dopamine and norepinephrine, in quantities large enough to affect host neurophysiology.

Production and recognition of neurochemicals that are more commonly associated with mammals by prokaryotic and eukaryotic microorganisms has led to a new understanding of an evolutionary-based mechanism by which microbes can influence host behavior and vice versa: namely, microbial endocrinology (Lyte, 2014a, 2014b; Lyte and Cryan, 2014b). Microbial endocrinology represents the intersection of the fields of microbiology and neurophysiology and had its beginnings in the demonstration that neurochemicals produced by the host during periods of stress, such as the biogenic amine norepinephrine, could dramatically increase the growth of bacteria both *in vitro* and *in vivo* (for review see Lyte, 2010).

Given that bacteria are prolific producers of neuroendocrine hormones, as well as other neuroactive compounds (Holzer and Farzi, 2014), it would seem reasonable to conclude that such bacterial production of neuroactive compounds within the gut lumen could influence either host-specific neural receptors within the gut or extra-intestinal neuronal sites following luminal uptake into the portal circulation. There are a number of reports that provide support that neurochemical production by bacteria within the gut can influence behavior in both human and animal model systems (Bravo et al., 2011; Messaoudi et al., 2011a; Collins et al., 2013). Most often, these reports employ probiotic bacteria, such as *Lactobacillus* or *Bifidobacterium*: many of the species belonging to these two genera are prolific producers of neurochemicals for which well-defined neural mechanisms are known and by which behavior may be modulated. Of particular interest, Bravo and colleagues (2011) observed reduced anxiety-like and depressive-like behavior in mice fed the probiotic strain *L. rhamnosus* (JB-1). Following probiotic administration, they were able to demonstrate changes in the levels of $GABA_{A\alpha 2}$ mRNA in those brain regions associated with the specific behavior (Bravo et al., 2011). Although they did not quantify the amount of GABA produced by the administered *L. rhamnosus* (JB-1) strain, the demonstration of a mechanism such as that mediated via central GABA receptor expression provides evidence that the ability of bacteria to influence behavior can occur through a neurochemical-mediated route.

And as to whether bacteria are capable of producing enough quantities of neurochemicals to affect behavior, a recent study that employed the GABA-producing *Lactobacillus brevis* FPA 3709 amply demonstrates that ability. In this functional food study, *L. brevis* was used to enrich black soybean milk with GABA, which was then fed to rats subjected to the FST (Ko et al., 2013). The FST, in which animals are placed in a water-containing glass cylinder and the duration of immobility before the animals begin to swim is measured, is a well-recognized test of depressive-like behavior. In this study, the GABA-enriched soybean milk significantly reduced the immobility time before the rats began to swim and was as effective as the selective serotonin reuptake inhibitor fluoxetine as an antidepressant (Ko et al., 2013). The use and design of probiotics based on a microbial endocrinology-based approach has also been proposed (Lyte, 2011).

Microbiota and Brain Imaging

Although much of the progress in understanding how the microbiota-gut-brain axis influences brain function and behavior has been in preclinical studies, work is now moving forward in human populations. Alterations in the microbiota-gut-brain axis have been implicated in brain-gut disorders such as functional gastrointestinal (GI) disorders (Mayer and Tillisch, 2011), inflammatory bowel diseases (Mayer et al., 2014), obesity, and metabolic syndrome (Yau et al., 2012). In addition, microbiota are also implicated in non-GI brain disorders, including anxiety and depression, multiple sclerosis, Alzheimer's disease, Parkinson's disease, and autism (Cryan and Dinan, 2012; Foster and McVey Neufeld, 2013; Naseribafrouei et al., 2014; Jiang et al., 2015; Mayer et al., 2015; Scheperjans et al., 2015). Results to date point to changes in microbiota composition and diversity in patient populations compared to healthy individuals: however, few studies have made direct links between gut microbiota and brain function. One approach to study gut-brain interactions in human populations is to combine manipulations of the gut microbiota with brain imaging and measures of symptoms of emotion (Tillisch et al., 2013). A recent report showed that probiotic ingestion affected brain functions in healthy women (Tillisch et al., 2013). In a double blind, randomized, controlled study, individuals received that test product—a commercially available fermented milk product that contained *B. animalis* subsp *lactis (B. Lactis)*, *Lactoccouc lactis* subsp *lactis*, *L. delbrueckii* subsp *bulgaricus*, and *Streptococcus thermophiles*—a non-fermented dairy product, or no treatment (Tillisch et al., 2013). This probiotic combination was previously shown to have no impact on the composition of the gut microbiota, but did modulate some metabolic pathways involved in polysaccharide degradation, including amino acid metabolism (McNulty et al., 2011). Interestingly, consumption of

the test product containing probiotics for 4 weeks was associated with reduced engagement of an extensive brain network in response to an emotion recognition task (Tillisch et al., 2013). The widely distributed brain network was increased in the no treatment group, not different in the individual who consumed the control product, and decreased in those who consumed the probiotic mixture (Tillisch et al., 2013). Ongoing work in the field of brain imaging includes an approach to connect gut microbial ecology (Saulnier et al., 2011) with large-scale brain networks (Irimia and Van Horn, 2013). Such approaches will aid in our ability to determine how the microbiome influences brain function and to potentially identify multiple mediators of the gut-brain axis.

Experimental Challenges Ahead

The past 5 years have seen an amazing increase in our knowledge of how bacteria signal to the brain and the implications this has for psychiatry. There are still many open questions, however. Firstly, the mechanisms of how the microbiota signals to the brain are only slowly being unraveled. The studies that have been performed to date have not yet conclusively demonstrated that a microbial endocrinology-based mechanism can account for the observed ability of the gut microbiota to influence behavior. We are at the very early stages of research, which will need to employ experimental rigor that must be employed to unequivocally demonstrate that it is the actual production of a neurochemical *in vivo* by a specific microorganism, and not a non-neurochemical aspect of the microorganism, such as a cell wall component interacting with immune cells in the gut, that is responsible for a specific change in behavior. Further, receptor-specific binding within the gut or extra-intestinal site must be demonstrated for the specific neurochemical produced by the microorganism. Recently, a step-by-step experimental approach was introduced to guide the experimental design for probiotics that seek to examine such microbial endocrinology–based mechanisms (Lyte, 2011). Such experiments are currently underway in a number of laboratories, and will provide a definitive answer.

Secondly, the individual components of bacteria that are mediating their effects need to be disentangled. As the field continues to consider composition and diversity of the microbiota in natural, clinical, and experimental settings, the evolving field of metabolomics is advancing and assisting in our ability to better understand the signaling cascades and roles of bacterial products.

Thirdly, as most of the studies to date have been in rodents, further human studies are needed to determine if bacteria-based interventions can indeed have a positive effect on mental health, a so-called psychobiotic effect (Dinan et al., 2013). Although some preliminary studies have focused on the altered composition of the microbiota in depression and autism, the time is now ripe for a comprehensive analysis of the microbiota in other disorders, including schizophrenia, anxiety, drug addiction, and eating disorders (Bach-Mizrachi et al., 2006; Dinan et al., 2014; Leclercq et al., 2014; Burokas et al., 2015; Fond et al., 2015; Nemani et al., 2015), followed by mechanistic studies that will determine if such changes have any causal relationship to psychiatric symptomatology.

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Statement of Interest

None.

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