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Neurotransmitter modulation by the gut microbiota

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Abstract

The gut microbiota – the trillions of bacteria that reside within the gastrointestinal tract – has been found to not only be an essential component immune and metabolic health, but also seems to influence development and diseases of the enteric and central nervous system, including motility disorders, behavioral disorders, neurodegenerative disease, cerebrovascular accidents, and neuroimmune-mediated disorders. By leveraging animal models, several different pathways of communication have been identified along the "gut-brain-axis" including those driven by the immune system, the vagus nerve, or by modulation of neuroactive compounds by the microbiota. Of the latter, bacteria have been shown to produce and/or consume a wide range of mammalian neurotransmitters, including dopamine, norepinephrine, serotonin, or gamma-aminobutyric acid (GABA). Accumulating evidence in animals suggests that manipulation of these neurotransmitters by bacteria may have an impact in host physiology, and preliminary human studies are showing that microbiota-based interventions can also alter neurotransmitter levels. Nonetheless, substantially more work is required to determine whether microbiota-mediated manipulation of human neurotransmission has any physiological implications, and if so, how it may be leveraged therapeutically. In this review this exciting route of communication along the gut-brain-axis, and accompanying data, are discussed.

The Human Gut Microbiota

Recent work has connected the human microbiota -- the trillions of bacteria that reside on or inside the body (Mayer et al., 2014) -- to many components of health and disease. Of particular importance is the gut microbiota, the complex bacterial community located in the gastrointestinal (GI) tract. Incredibly, not only has the gut microbiota been found to be essential for maintaining metabolic and immune health (Lynch and Pedersen, 2016), but of relevance to this review, there is also amassing evidence that the gut microbiota influences brain development (Diaz Heijtz et al., 2011), neurogenesis (Ogbonnaya et al., 2015), and interacts with the enteric and central nervous systems (ENS and CNS, respectively) via communication along the "gut-brain-axis" (Fung et al., 2017). The majority of this work has been performed in animals models, with preliminary studies showing the gut microbiota

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having a role in intestinal motility disorders (Ge et al., 2017), visceral pain (Luczynski et al., 2017), depression (Kelly et al., 2016; Zheng et al., 2016), anxiety (De Palma et al., 2017), Parkinson's Disease (Sampson et al., 2016), Alzheimer's Disease (Minter et al., 2016), Multiple Sclerosis (MS) (Berer et al., 2017; Cekanaviciute et al., 2017), ischemic stroke (Benakis et al., 2016), and symptomologies of Autism Spectrum Disorder (ASD) (Hsiao et al., 2013). However, while these findings are exciting, the mechanisms behind these influences are still being elucidated.

Identifying Mechanisms of Communication Along the Gut-Brain-Axis

An attractive and simple exploratory technique to determine whether the microbiota may be involved in a disease is to eliminate bacteria from an animal (either through treatment with a combination of broad-spectrum antibiotics, or use of germ free lines/facilities), and determine if end points in a model of interest change. Using this approach, a seminal 2004 study found that germ free mice exhibited an increased response to induced stress via the restraint model, and that this behavioral alteration could be restored by recolonizing these animals with a complete microbiota (via stool transplant) or by monocolonization with *Bifidobacterium infantis* (but not *Escherichia coli*) (Sudo et al., 2004). Since then, bacteria-depleted animals have been shown to exhibit key differences in multiple ENS/CNS-related endpoints, including those of intestinal motility (Dey et al., 2015; Yano et al., 2015), visceral pain (Luczynski et al., 2017), autism spectrum disorder (Hsiao et al., 2013), neurodegenerative disease (Harach et al., 2017; Minter et al., 2016), depression (Kelly et al., 2016; Zheng et al., 2016), and MS (Berer et al., 2011). Microbiota depleted models have also been used to determine whether transferring the gut microbiota of a person suffering from ENS/CNS disease to animals via fecal transplant can transfer disease symptomologies (stool from healthy patients is used as a control for these studies). Incredibly, adoption or potentiation of ENS/CNS disease endpoints after human-to-animal fecal transplant has been observed for slow transit constipation (Ge et al., 2017), depression (Kelly et al., 2016; Zheng et al., 2016), anxiety (De Palma et al., 2017), MS (Berer et al., 2017; Cekanaviciute et al., 2017), and Parkinson's Disease (Sampson et al., 2016).

Importantly, a major goal of any microbiome study is to move beyond correlation, and parse out potential routes of communication/interaction between the host and its resident bacteria. The above-mentioned observations suggest something in the microbiota is influencing ENS/CNS diseases, and systematic approaches have been leveraged to parse out what component of that microbiota (e.g. a bacterium, small molecule, protein) are responsible (Figure 1). This has resulted in the identification of several different mechanisms for gut bacteria to influence the nervous system (Figure 2), including altering the activity of the stress-associated hypothalamic–pituitary–adrenal (HPA) axis (Sudo et al., 2004); vagal nerve stimulation (Bonaz et al., 2018; Bravo et al., 2011); secretion of short chain fatty acids (which can activate microglial cells (Erny et al., 2015), as well as affect permeability of the blood brain barrier (Braniste et al., 2014)); or, and the focus of the remainder of this review, the ability of the gut microbiota to modulate neurotransmitters directly or through host biosynthesis pathways.

Neurotransmitters and the Microbiota

Abbreviations. Gastrointestinal tract (GI); Enteric Nervous System (ENS), Central Nervous System (CNS); Multiple Sclerosis (MS); gamma-aminobutyric acid (GABA); hypothalamic-pituitary-adrenal (HPA); *Escherichia coli* O157:H7 (EHEC); Enterochromaffin cells (ECs)

When considering how the microbiota may interact with the nervous system, perhaps the most obvious scenario would be through modulation of host neurotransmitters and/or related pathways. Indeed, bacteria have been found to have the capability to produce a range of major neurotransmitters (Table 1), so many in fact, it was proposed as its own field of study decades ago – microbial endocrinology (Lyte, 1993). Below is a summary of a selection of neurogenic amines and amino acids, as substantial evidence has accumulated around a microbiota-mediated influence of those compounds. However, and outside the scope this of review, the microbiota has the potential to influence levels of other neurotransmitters, including histamine (Hegstrand and Hine, 1986), gasotransmitters (Oleskin and Shenderov, 2016), neuropeptides (Holzer and Farzi, 2014), steroids (Tetel et al., 2018), and endocannabinoids (Cani et al., 2016), among others (Neuman et al., 2015).

Dopamine and Norepinephrine

Dopamine is one of the major neurotransmitters in reward-motivated behavior, and is a precursor for other catecholamines, like norepinephrine and epinephrine. Norepinephrine is historically known for its role in arousal and alertness in the waking state as well in sensory signal detection, but more recent work has found it is also involved in behavior and cognition, like memory, learning, and attention (Borodovitsyna et al., 2017).

Interestingly, it appears bacteria also respond to and/or produce these catecholamines. For example, pathogenic *Escherichia coli* O157:H7 (EHEC) has an increased growth rate in the presence of dopamine and norepinephrine (Freestone et al., 2002), as well as exhibits increased motility, biofilm formation, and virulence in the presence of norepinephrine (Bansal et al., 2007). In addition to EHEC, the pathogens *Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, Shigella sonnei*, and *Staphylococcus aureus* were all found to have improved growth *in vitro* in the presence of norepinephrine, which may be due to an involvement in iron acquisition (O'Donnell et al., 2006). Several bacteria have been also shown to produce dopamine and norepinephrine (Table 1). *In vitro*, *E. coli, Proteus vulgaris, Serratia marcescens*, *Bacillus subtilis*, and *Bacillus mycoides* were found to harbor relatively high levels (0.45–2.13 mM) of norepinephrine in their biomass (Tsavkelova et al., 2000). Physiologically, it appears norepinephrine is produced as a quorum sensing molecule in bacteria (Sperandio et al., 2003), but production of dopamine is not yet understood.

While it has not been confirmed that the microbiota modulates norepinephrine or dopamine *in vivo*, there is accumulating evidence suggesting it may, or at least play a role in host biosynthesis/catabolism. With regards to norepinephrine, a recent study leveraging germ free animals found that mice without bacteria have substantially reduced levels of norepinephrine in the cecal lumen (35 ± 5ng/g compared to 3.8 ± 1.3 ng/g) and in the tissue (115 ± 14 ng/g vs. 5.0 ± 0.5 ng/g), and that cecal levels of norepinephrine could be restored via colonization

with a microbiota or with a mixture of 46 *Clostridia* species (Asano et al., 2012). This finding strongly suggests the microbiota influences levels of norepinephrine in the lumen, but whether the bacteria were producing norepinephrine directly or modulating host production was not determined. Beyond the gut, germ free mice also display an increased turnover rate of dopamine and norepinephrine (as well as serotonin) in the brain (Diaz Heijtz et al., 2011), which could generally reduce pools in systemic circulation independent of microbial production (although factors influencing that increased turnover rate remain to be determined). The general ability of the microbiota to influence catecholamine systems may be functionally important, as it was reported in mice that depletion of the microbiota with non-absorbable antibiotics increased sensitivity to the behavioral effects of cocaine – an effect that with associated with elevated activity of the D1 dopamine receptor *Drd1* and the GluR2 AMPA receptor *Gria2* in the nucleus accumbens (Kiraly et al., 2016). Interestingly, the behavioral response to cocaine was normalized in antibiotic treated animals upon supplementation with short chained fatty acids, major biproducts of microbial fermentation, suggesting an indirect path for the microbiota to influence reward behavior.

Serotonin

Serotonin is involved in regulating numerous physiological processes, including gastrointestinal secretion and peristalsis, respiration, vasoconstriction, behavior, and neurological function (Berger et al., 2009; Gershon and Tack, 2007). While serotonin is broadly used throughout the body, 90–95% of serotonin resides in the gastrointestinal tract, mostly in epithelial enterochromaffin cells (ECs)(Gershon and Tack, 2007).

Given the abundance of serotonin in the GI tract, it is perhaps not surprising that an expanding list of literature is linking the microbiota to host levels of serotonin. In germ free animals, there is a significant reduction of serotonin in the blood and colon of mice compared to controls (Wikoff et al., 2009), a feature which can be restored via recolonization with a microbiota or with a consortium of spore-forming species. Notably, while several strains of bacteria are reported to produce serotonin (Table 1), such capabilities have not been identified in the gut microbiota. Instead the alteration of host serotonin levels appears to mediated via secretion of small molecules (like short chain fatty acids or secondary bile acids) that signal ECs to produce serotonin via expression of tryptophan hydroxylase (Yano et al., 2015). There is also evidence that the entrance of gut tryptophan into the immune-driven kynurenine pathway may play a major role serotonin dysregulation and the concomitant physiological consequences (for extensive review, see (Kennedy et al., 2017)). In the brain, however, the impact of the microbiota on serotonin is not as clear – in germ free animals, while serotonin turnover is increased (Diaz Heijtz et al., 2011), there are generally higher serotonin levels in the hippocampus of male mice (Clarke et al., 2013).

Gamma-aminobutyric acid (GABA)

GABA is the major inhibitory neurotransmitter of the central nervous system, and it and its receptors are widely distributed throughout the mammalian host. Substantial literature supports the link between altered GABAergic neurotransmission and numerous CNS disorders, including behavioral disorders, pain, and sleep (Wong et al., 2003), as well in the

disruption of important functions of the ENS, such as intestinal motility, gastric emptying, nociception, and acid secretion (Hyland and Cryan, 2010).

Bacteria have been known to be able to consume or produce GABA for decades. For consumption, the major pathway is the GABA shunt, in which GABA is converted to succinate for entrance into the TCA cycle (Feehily and Karatzas, 2013). Organisms like *E. coli* can grow on GABA as a sole carbon and nitrogen source (Dover and Halpern, 1972), but the general ability of the microbiota to consume GABA has not been explored. Production has been better studied, and a broad diversity of bacteria have been reported to produce GABA (Table 1). Unlike the other neurotransmitter mentioned, production of GABA has a well-understood physiological purpose in these organisms -- secretion of GABA serves as a mechanism to decrease intracellular pH via the glutamate acid resistance system (Feehily and Karatzas, 2013).

The microbiota seems to influence circulating GABA levels, as germ-free animals have substantially reduced luminal and serum levels (but not cerebral levels) of GABA (Matsumoto et al., 2013). Several commensal organisms have been reported to produce GABA, including members of the *Bifidobacterium* and *Lactobacillus* genera (Table 1). Of those known, *Lactobacillus rhamnosus*s JB-1 is most often cited, as it was found its introduction into mice reduced depressive- and anxiety-like behavior in a vagus-dependent manner, with accompanying changes in cerebral GABAergic activity (Bravo et al., 2011). Notably, the ability of *Lactobacillus rhamnosus* JB-1 to produce GABA was not tested, so it cannot be definitively concluded the observed reponse was due to GABA secretion by this strain. Nonetheless, the ability of microbiota-mediated GABA to positively influence the host was reinforced in a more recent study, in which oral supplementation of *Bifidobacterium breve* NCIMB8807 pESHgadB, a strain engineered to produce GABA via overexpression of glutamate decarboxylase B, reduced sensitivity to visceral pain in a rat model (Pokusaeva et al., 2017). Importantly, the wild-type strain, *Bifidobacterium breve* NCIMB8807, had no impact on the visceral pain endpoint, confirming the benefit was due to GABA secretion (Pokusaeva et al., 2017).

In humans, preliminary reports suggest that manipulating the human microbiota may impact GABA levels. Dietary interventions are well known for their ability to alter the composition and function of the gut microbiome (David et al., 2014), and a ketogenic diet was shown to increase GABA levels in the CSF of children with refractory epilepsy, a response correlated with improvement of symptoms (Dahlin et al., 2005). More conclusively, in a recent fecal transplant study, GABA was found to be the most altered metabolite in obese patients receiving allosteric fecal transplant from lean donors (Kootte et al., 2017), a finding which was associated with improved insulin sensitivity. Nonetheless, how GABA produced by the microbiota may be involved in human health and disease remains to be determined.

Prospectus

While accumulating evidence suggests the gut microbiota can influence the nervous sytem, more work is required to validate potential mechanisms. Modulation of neurotransmission seems to be a likely route of communication along the gut-brain-axis, and animal

experiments that couple microbiome intervention with neurotransmitter receptor antagonists will further confirm these pathways. Additionally, as the majority of existing work has been performed in animals, there is a strong need for well-designed human cohorts that leverage broad-omic surveys as well as traditional means to study ENS/CNS disease, like imaging (Tillisch et al., 2017). By understanding these communication routes and their associations with disease phenotypes, microbiome-mediated interventions could be designed to manipulate these targets and potentially treat diseases with major unmet needs, like those affecting the ENS/CNS.

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HIGHLIGHTS

- The human microbiota has been linked to numerous components of health and disease
- Gut bacteria can influence diseases of the enteric and central nervous systems
- Bacteria have the capability to produce or consume neurotransmitters
- Neurotransmitter modulation is a likely communication route along the gut-brain-axis

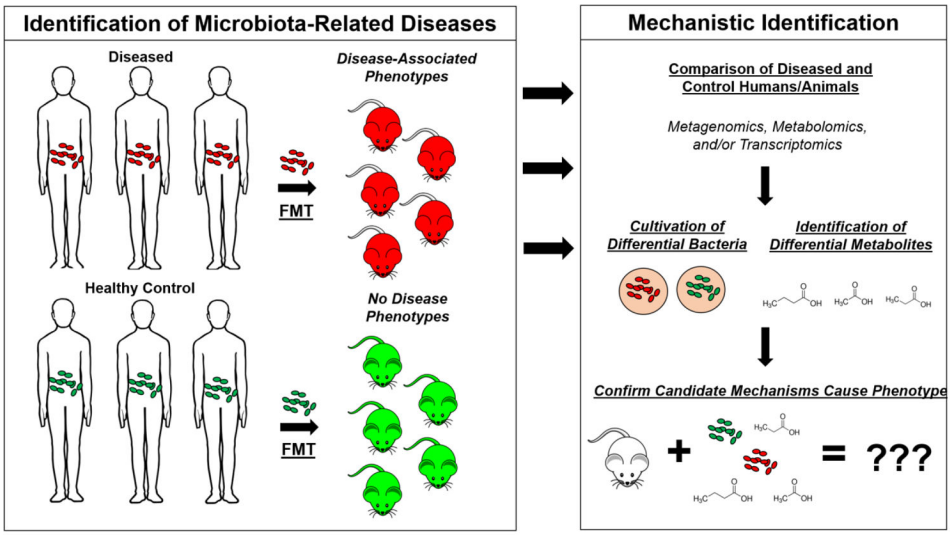

FIGURE 1. From microbiome discovery to mechanism

An example of the path from observing the microbiome may be involved in a disease to a mechanistic understanding. One approach to explore whether or not the microbiota is involved in a given disease is to transfer the gut microbiota from a patient suffering a disease into an animal via fecal microbiome transplant (FMT) and then pass that animal through the appropriate disease model. If transplantation of the gut microbiota from a diseased patient affects the end points in the model (but transplant of a microbiota from health controls do not), effort should go into understanding a potential underlying mechanism. Generally, this is achieved by using a broad -omic approaches, ideally through the combination of metagenomics, metabolomics, and/or transcriptomics of host stool and other tissues. By comparing the results from disease-presenting animals to controls, candidate bacterium and/or metabolites that may be influencing the disease end points can be identified. If introduction of the candidate trigger organism(s) or metabolite(s) results in the same change in end points, it is likely they are involved in presentation of the phenotypes.

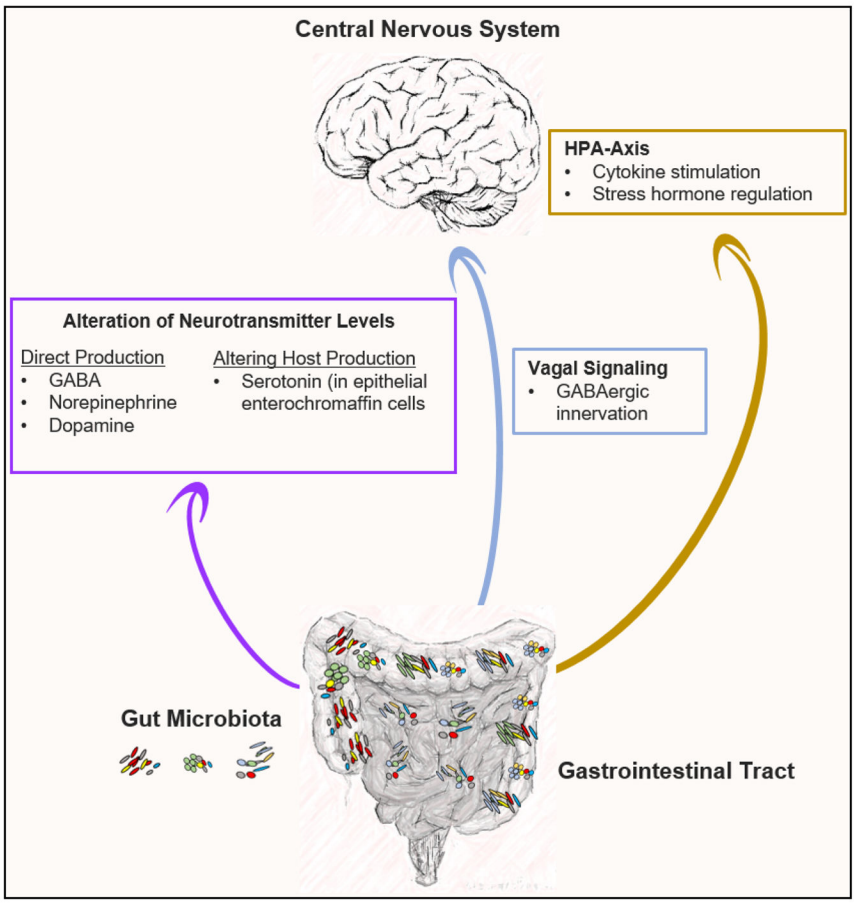

FIGURE 2. Communication routes of the gut microbiota to the brain

The gut microbiota has been found to communicate with the brain through several different mechanisms. This includes production of neurotransmitters or modulation of host neurotransmitter catabolism, innervation via the vagus nerve, or activation of the HPA axis.

TABLE 1
Representative neurotransmitter producing bacteria

A number of bacteria have been reported to be able to produce a range of mammalian neurotransmitters. This table was curated to include only one organism per species, and parenthesis indicate strain when available. Much of the information listed here was taken from Dhakal *et al.*, 2012 and Clarke, *et al.* 2014, with more recently reported neurotransmitter producing organisms being added.

Neurotransmitter	Bacterial Strain	Reference
Dopamine	Bacillus cereus	Tsavkelova et al., 2000
	Bacillus mycoides	Tsavkelova et al., 2000
	Bacillus subtilis	Tsavkelova et al., 2000
	Escherichia coli	Tsavkelova et al., 2000
	Escherichia coli (K-12)	Shishov VA, 2009
	Hafnia alvei (NCIMB, 11999)	Özoğul, 2004
	Klebsiella pneumoniae (NCIMB, 673)	Özoğul, 2004
	Morganella morganii (NCIMB, 10466)	Özoğul, 2004
	Proteus vulgaris	Tsavkelova et al., 2000
	Serratia marcescens	Tsavkelova et al., 2000
	Staphylococcus aureus	Tsavkelova et al., 2000
Noradrenaline	Bacillus mycoides	Tsavkelova et al., 2000
	Bacillus subtilis	Tsavkelova et al., 2000
	Escherichia coli (K-12)	Shishov VA, 2009
	Proteus vulgaris	Tsavkelova et al., 2000
	Serratia marcescens	Tsavkelova et al., 2000
Serotonin	Escherichia coli (K-12)	Shishov VA, 2009
	Hafnia alvei (NCIMB, 11999)	Özoğul, 2004
	Klebsiella pneumoniae (NCIMB, 673)	Özoğul, 2004
	Lactobacillus plantarum (FI8595)	Özoğul, 2012
	Lactococcus lactis subsp. cremoris (MG 1363)	Özoğul, 2012
	Morganella morganii (NCIMB, 10466)	Özoğul, 2004
	Streptococcus thermophilus (NCFB2392)	Özoğul, 2012
GABA	Bifidobacterium adolescentis (DPC6044)	Barrett et al., 2012
	Bifidobacterium angulatum (ATCC27535)	Pokusaeva et al., 2017
	Bifidobacterium dentium (DPC6333)	Barrett et al., 2012
	Bifidobacterium infantis (UCC35624)	Barrett et al., 2012
	Lactobacillus brevis (DPC6108)	Barrett et al., 2012
	Lactobacillus buchneri (MS)	Cho et al., 2007
	Lactobacillus paracaseiNFRI (7415)	Komatsuzaki et al., 2005
	Lactobacillus plantarum (ATCC14917)	Siragusa et al., 2007
	Lactobacillus reuteri (100-23)	Pokusaeva et al., 2017
	Lactobacillus rhamnosus (YS9)	Siragusa et al., 2007

Neurotransmitter	Bacterial Strain	Reference
	Lactobacillus. delbrueckiisubsp. bulgaricus (PR1)	Siragusa et al., 2007
	Monascus purpureus (CCRC 31615)	Su et al., 2003
	Streptococcus salivarius subsp. thermophilus (Y2)	Yang et al., 2008
Acetylcholine	Lactobacillus plantarum	Stanaszek et al., 1977
Histamine	Citrobacter freuindii	Kim et al., 2001
	Enterobacter spp.	Kim et al., 2001
	Hafnia alvei (NCIMB, 11999)	Özoğul, 2004
	Klebsiella pneumoniae (NCIMB, 673)	Özoğul, 2004
	Lactbacillus plantarum (FI8595)	Özoğul, 2012
	Lactobacillus hilgardii	Landete et al., 2007
	Lactobacillus mali	Landete et al., 2007
	Lactococcus lactis subsp. cremoris (MG 1363)	Özoğul, 2012
	Lactococcus lactissubsp. lactis (IL1403)	Özoğul, 2012
	Morganella morganii (NCIMB, 10466)	Özoğul, 2004
	Oenococcus oeni	Landete JM, 2005
	Pediococcus parvulus	Landete et al., 2007
	Streptococcus thermophiles (NCFB2392)	Özoğul, 2012