Brain Research 1693 (2018) 128–133

Contents lists available at ScienceDirect

Brain Research

journal homepage: www.elsevier.com/locate/bres

Research report

Neurotransmitter modulation by the gut microbiota

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ARTICLE INFO

Article history:
Received 16 October 2017
Received in revised form 8 March 2018
Accepted 13 March 2018

Keywords:
Human microbiota
Gut microbiota
Gut-brain-axis
Neurotransmitters

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.

1. 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 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.

2. 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

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

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https://doi.org/10.1016/j.brainres.2018.03.015
0006-8993/

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 (Fig. 1). This has resulted in the identification of several different mechanisms for gut bacteria to influence the nervous system (Fig. 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.

3. Neurotransmitters and the microbiota

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 key data for 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).

3.1. 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).

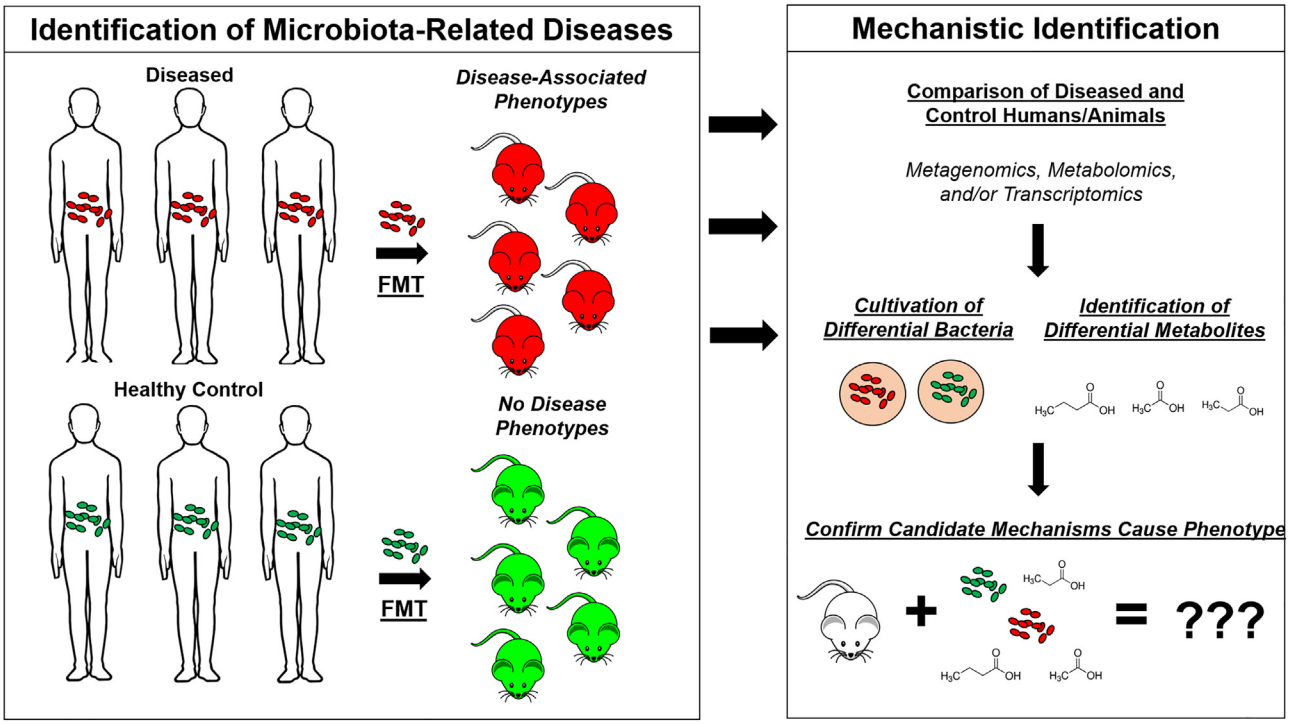

Fig. 1. From microbiome discovery to mechanism. An example of the path from observing the microbiome may be involved in a disease to a mechanistic understanding. One approach to explore whether or not the microbiota is involved in a given disease is to transfer the gut microbiota from a patient suffering 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 healthy 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 bacteria 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.