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Mechanisms, Phenotypes, and Translational Applications of the Gut-Brain Axis in Neurological Function Regulation

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Abstract. The gut microbiota functions as an endocrine-like system that engages in two-way communication with the brain through the gut-brain axis (GBA). It consists of largely endocrine, some neural but also immunological pathways. Data have begun to speculate that dysbiosis may result in behavioral abnormalities, including depression and anxiety the pathological basis of which may be based on neuroinflammation and derivatives of impaired synaptic plasticity and that it may accelerate neurodegenerative disease like Alzheimer's disease (AD). Dysbiosis, by operating on certain molecular pathways closely linked to factors, and other mechanisms, empowers the gut microbiome as a potential biomarker for neurological disease with potential for manipulation of the microbiota - probiotics, dietary modulation and FMT, as disease prevention and therapy. Current studies are challenged by a lack of discerning causality. Future studies must now translate basic findings to patients through trans-disciplinary collaboration to define targeted manipulation of the gut microbiota to promote brain health.

Keywords: Brain-Gut Axis, Gut Microbiota, Neuroinflammation

1. Introduction

The gut microbiota functions as a crucial endocrine organ, playing a key role in maintaining systemic homeostasis. It carries out a variety of important and necessary jobs in the human body. For instance, besides aiding digestion and metabolism it also influences the rate of growth and the state of maturity of epithelial cells. In addition, the colonization of mucosal surfaces and the production of antimicrobial compounds contribute to host defense and support immune system homeostasis [1]. More recently, relationship with brain function and neuromodulation has become a popular subject of research. In fact, the GBA represents an intricate two-way signaling network linking the gastrointestinal (GI) tract with the central nervous system (CNS) through neural, endocrine, and immune pathways [2]. The communication is such that while it is complex it also allows the gut to redirect or indirectly alter our mood, our intellectual capability and even the central nervous system itself. Microorganisms in the gut excrete a variety of metabolites and neurotransmitters namely, peptides, gut hormones, cytokinin and neuroactive treasure of microbial metabolites contribute to the neurohomeostatic equilibrium. Some of these microbial secretions can transverse a number of barriers from the intestinal to the blood-brain barrier, regulating key brain

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functions of neurogenesis, neuroinflammation and synaptic plasticity. However, dysbiosis of the gut is so widespread making it important just how gut dysbiosis caused by stress, diet, antibiotics and the like can lead to various neurological injuries [1]. There pathologic significance of gut microbes unjacketing with respect to brain health cannot perhaps be overstated. More and more evidence shows the fact that change in gut composition of gut due to the gut microbiome pathogens predating or occurring alongside the onset of neurologic signs including the gut microbiota may actively participate in evolving or modulating disease onset and progression. What the mechanics of dysbiosis of the gut that likely drives the other than disease of the animal's brain couldn't be surmised by even now.

Significant knowledge gaps remain regarding the GBA. Although there are animal models utilized for research on the gut-brain link, it remains limited to rodents and dogs, and the microbiota across species should also be aimed to be compared. Explanatory mechanisms of the GBA remain vague, and the transition from correlation to suggesting causation is still tenuous. Most are merely suggestive studies and there is a lack of methodical investigations testing the directionality of these associations through faucal microbiota transplantation, germ free models or interventions with specific bacteria. Thus, the goals of this work are to critically assess the mechanisms of the gut-brain axis, summarize commonly found neurological diseases resulting from gut dysbiosis in animal models, and provide the outlook and possible future use of gut-brain research for precision veterinary medicine and beyond.

2. Core communication mechanisms of the GBA

The GBA can be viewed as a bidirectional communication system mapped out to utilize endocrine, neural, and immunologic pathways that allow for both ascending and descending control.

Endocrine control can be described as hormone signaling between the gut and brain. The gut secretes hormones that may mediate that signaling. There are several hormones secreted from the gut that are collectively referred to as GI hormones, and include gastrin, GLP-1, glucagon, etc. These GI hormones influence digestion and are absorbed to also affect signaling in the brain via the blood. Short-chain fatty acids (SCFAs) are a crucial class of metabolites generated by the gut microbiota. SCFAs can promote restoration of impaired blood-brain barrier (BBB) function by restoring tight junction proteins. SCFAs improve the paracellular permeability decrease by influencing the transcription, intercellular localization, or proteolytic degradation of tight junction proteins [1]. The gut microbiota also directly or indirectly impacts the native production of several neurotransmitters like serotonin and dopamine. Nearly 95% of systemic serotonin production occurs in enterochromaffin cells, which represent the dominant neuroendocrine cell population within the gastrointestinal tract [3]. These neurotransmitters regulate gastrointestinal motility and are also critically involved in emotional regulation.

Neural mechanisms are pivotal in this GBA communication pathways. Neural mechanisms constitute an essential component of the GBA, supporting bidirectional communication mainly through two routes: the vagus nerve and the enteric nervous system (ENS). The vagus nerve belongs to the peripheral nervous system (PNS) and consists predominantly of afferent fibers (approximately 80%), with the remaining 20% being efferent fibers, forming a major signaling route to the brain [2]. Vagal afferent fibers receive input from the gut microbiota and their metabolites and transmit these signals to multiple brain centers, contributing to sensations such as satiety or gastric discomfort, whereas efferent motor fibers convey regulatory commands from the brain to the intestine. In contrast, the ENS is often termed the "second brain" due to its autonomous function. The ENS is part of the autonomic nervous system, forming a "neural net" along the wall of the intestinal tract

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and regulating food transport, blood to intestinal space, nutrients, and immune defense among others. It can also co-ordinate local gut activity without the CNS which is a hallmark part of its justify to its dual identity as the second brain. Thus, the vagus nerve and ENP being the fast, two-way communication system of "neural information highway" between the gut and brain, which act as to directly regulate activity at the CNS level in rapid fashion by signals from the microbiota.

Immune mechanisms underlie the GBA - gut microbes can activate immune cells in the gut and produce a plethora of inflammatory mediators and cytokines, or recruit many chemokines that trigger systemic inflammation, as well as neuroinflammation in the brain [4]. Indeed, in the brain, cytokines act on microglia (immune cells of the CNS), astrocytes and neurons triggering neuroinflammatory responses that disrupt neurotransmitter synthesis and signal transmission, impairs hypothalamic-pituitary-adrenal (HPA) axis function and increase risk for mood disorders, cognition defects, behavior abnormalities [5]. That is, they impact on mood and behavior by regulating the relationship between inflammatory responses and the nervous system.

3. Typical neurological phenotypes of GBA dysregulation in animal models

A wide range of investigations employing germ-free animals, fecal microbiota transplantation, and gene-edited models demonstrates that disruptions in gut microbial composition are associated with diverse neurological phenotypes [5,6]. Ranging from behavioral changes to pathological alterations in such animals, these phenotypes testify to the vital nature of the GBA.

The most notable phenotype we see here of dysbiosis is behavioral change, closely tied as it is to emotional disturbances and social deficiencies, be they in humans or animals. One experiment by Kelly JR et al, saw researchers transplant fecal microbiota from depressed patients into germ free rats, forcing them into a depression and attempting to change their behavior by disrupting tryptophan metabolism [5]. This paper aided in promoting tryptophan metabolism as a major component of GBA. It must be noted however that human to animal FMT are flawed models as we cannot therefore control for environmental factors seen in humans. Additional studies report that alterations in gut microbial balance are linked to various anxiety-related disorders in both animal models and humans, potentially through changes in serotonin levels, immune system dysregulation, and modulation of GABA signaling [7]. A number of papers from animal models to humans goes on to show how GBA dysregulation affects our nervous system through a multistage network comprising microbes, metabolites, immune cells and neural signaling resulting in phenotypes of neurological information processing.

These behavioral alterations are driven by significant pathological changes at the cellular and molecular levels within the brain, providing evidence for the gut-brain connection.

Neuroinflammation is a commonly studied pathological phenotype. Peripherally induced dysbiosis generates proinflammatory signals including lipopolysaccharide (LPS) and cytokines that enter the brain within the circulation or via neural pathways, stimulating microglia and astrocytes, before being excreted by activated microglia as proinflammatory factors disrupting neuronal function (IL-1β, IL-6, TNF-α etc.) [1].

Impaired synaptic plasticity is also a significant pathological feature. In experiments conducted with Sprague-Dawley rats, the effects of the gut microbiota-derived metabolite trimethylamine N-oxide (TMAO) were investigated. Using the water maze, they demonstrated that TMAO induces hippocampus dependent learning and memory deficits that occurs through potentiation of GSK-3β activity and is associated with impaired synaptic plasticity [8]. Consequently, microbiota dysbiosis is believed to modulate synaptic plasticity to promote cognitive impairment. Other models of neurodegenerative diseases show that gut dysbiosis can enhance the pathology. For instance, in

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multiple animal models of AD and PD, gut dysbiosis influences disease onset and progression by potentiating β-amyloid deposition and tau phosphorylation and aggregation, as well as abnormal α-synuclein spreading [6]. In conclusion, intestinal dysbiosis promotes a cesspool of neuroinflammation, impaired synaptic plasticity and neurodegenerative lesions, all of which provide important pathological evidence of GBA dysregulation in animal models.

4. Interactions between gut microbiota and neurotrophic factors: the underlying mechanism of GBA

Although animal models have established that impairment of the gut-brain axis results in various neurobehavioral abnormalities, the precise molecular mechanisms through which gut microbes influence brain activity are still not well understood. Methylated CpG-binding protein 2 (MeCP2) exemplifies an important interface of this kind. Playing a crucial role in brain development, MeCP2 is such that its loss of function is directly responsible for Rett syndrome [10]. However, whether MeCP2 is the cause or consequence of the gut microbiota is variable. MeCP2 is found expressed in intestinal neurons or enteroendocrine cells, impacting gut motility, mucus secretion and immune regulation, which changes the intestinal microenvironment. Junfang Wang and colleagues found that MeCP2-overexpressing transgenic mice displayed dysbiosis of their gut microbiota. This microbial imbalance is associated with alterations in multiple neurotransmitters whose metabolic pathways are influenced by microbial activity in MeCP2 duplication syndrome, a neurodevelopmental disorder characterized by autistic features [9]. It is not known if microbiota intervention could ameliorate the corresponding neurological symptoms in MeCP2 deficient animal models, but this study does lend further tentative credence to implicating MeCP2 and its role in GBA.

The other regulatory factor such as BDNF are also important to GBA signaling. BDNF neurotrophic has effects on synapse development and plasticity. Reduced levels of the intestinal probiotic Akkermansia muciniphila have been linked to downregulation of serotonin (5-HT) levels in the intestine. This process impairs vagal signaling and compromises intestinal barrier integrity, permitting lipopolysaccharide to induce systemic inflammatory responses [10]. At the same time hepatic expression of 5-HT2A/2B receptors are upregulated and liver fibrosis deteriorates. This is a result of lower BDNF level in the hippocampus and cognitive function [10]. This shows the gut microbiota regulates BDNF expression and affects neuroplasticity.

Numerous neuroregulatory factors, such as MeCP2 and, in particular, BDNF are examples of neuroregulatory molecules interacting with the gut microbiota. Collectively, these interactions demonstrate the capacity of the gut microbiota to directly affect the CNS through engagement with specific targets and receptors, as well as by modulating the expression and activity of neurotrophic and epigenetic regulatory molecules. Whether acting directly or indirectly, the findings demonstrate that gut microbes can influence CNS activity through various receptors as well as signaling pathways.

5. Application and transformation

Research on the GBA is fast-tracking from bench to bedside, opening new diagnostic and therapeutic avenues, mainly for human medicine but also giving insight in animal models, which can help us understand complex animal behavior and aid in treating neuropsychiatric disorders, thus directly leading to a host of innovative diagnostic and therapeutic strategies.

Gut microbiome as a new biomarker and new approaches to diagnosis: in models of depression, for instance, a decrease in Faecalibacterium species associated with an increase in

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Enterobacteriaceae and Alistipes species and presence of substances including 5-HT could be a novel diagnostic approaches for neuropsychiatric disorders [11]. Another study demonstrated that gut microbiota–mediated modulation of the stress response is influenced by circadian rhythmicity [12]. This points to the potential for predicting assess stress states or aberrant behavior in farm animals (pigs, poultry) using changes in microbial community in animal husbandry.

Microbiome-targeted modulation is increasingly suggested as a novel strategy for disease treatment. Probiotics, currently available on the market and widely used, are biological products from nonpathogenic microorganisms that act by strengthening the intestinal barrier, have anti-inflammatory effects, and demonstrate neuroprotective activity. The primary bacterial genera employed as probiotics are Bifidobacterium, Lactobacillus, Bacillus, Streptococcus, and Enterococcus [13]. In contrast FMT has also been used clinically, where it has been found highly successful in treating several diseases, among which inflammatory bowel disease and multiple sclerosis. FMT has showed promising therapeutic potential in cancer cases too. Diet-based tailoring interventions to modulate the gut microbiota demonstrate another microbiome-based therapy. Diet is the first tool for shaping the microbiota. It is increasingly thought that an optimized combination of dietary components-including proteins, dietary fiber, omega-3 fatty acids, polyphenols, and other functional supplements-can shape the intestinal microbiota in ways that are beneficial to nervous system function. However, it should be noted that huge individual differences prevent cultivation of a given microbiota in a precise and specific manner. This is actually a simple preventive and therapeutic strategy at a low cost.

6. Conclusion

This article gives a concise overview of how gut microbiota neurological function via the GBA, conventional neurological phenotypes of dysbiosis in animal models, underlying molecular mechanism/s and associated translational hopes.

The review suggests that the gut microbiota engage in intricate communication with the brain through three generic, bidirectional communication pathways: endocrine, neural, and immune pathways. Such communication pathways permit the microbiota to powerfully affect the host(s) mood, cognition, behavior, and nervous-system homeostasis. Studies using animal models show that disruptions in gut microbial balance give rise to a range of distinct neurobehavioral phenotypes, which appears at the behavioral level as depression- and anxiety-like behavior and social deficits, and at the pathological level as neuroinflammation, impaired synaptic plasticity, and acceleration of neurodegenerative disease. These phenotypic changes are manifested via interaction between important neuroregulatory factors (MeCP2 and BDNF), and the gut microbiota that regulates their expression and action using both metabolites (eg. short-chain fatty acids, neurotransmitters) and immune signals to effect neurodevelopment, synaptic function, and neuronal plasticity.

Building on this knowledge, relevant translational applications are now unfolding. The gut microbiome emerges as a promising novel biomarker for diagnosing neuropsychiatric disorders. Concurrently, a variety of approaches have been developed to modulate the microbiome, such as dietary interventions, probiotics, and prebiotics, with the goal of guiding the local microbial community toward a more favorable state, while other more direct and efficacious approaches such as microbiota FMT, constitute a distinct category of therapeutic strategies aimed at preventing and treating neuropsychiatric disorders while improving behavioral outcomes in animal models.

Despite these advances, GBA research has numerous limitations and challenges. For example, while several studies have been able to correlate the gut microbiota to neurological functions or disease states, establishing causality/proof is not always clear-cut. Current research, however, is still

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largely reliant on rodent models, but there are differences between species with regards to gut microbiota composition, the nervous system in terms of structure and function, and also immune responses, so caution must be taken in simply extrapolating findings directly from animal studies to humans or other animals. Further, the complexity of the signaling pathways of GBA and clarity of the mechanisms to many of these remains to be discovered.

Future mechanistic studies should seek to incorporate multiple communication pathways and, using systems biology approaches, build dynamic network models of GBA. Sharper animal models (including the further development of non-human primates, organoids like gut organoids “brain organoids” that simulate human or even species-specific a physiological and pathological environment) needs wise, since GBA research requires a true intersection of microbiology, neuroscience, immunology, endocrinology, nutrition science, veterinary medicine and clinical medicine, the benefits of interdisciplinary cross-pollination of fundamental discoveries into clinical realization will be repaid many times over.

In conclusion, studies exploring the GBA can be opening new horizons in gut health and disease. Despite the persistence of many unresolved scientific questions, targeted manipulation of the gut microbiota-supported by continued advances in mechanistic understanding and the development of improved experimental models-is expected to become a critical approach for preventing and treating brain disorders.

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