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Microbiome and gut-brain axis affecting stress behavior

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Abstract:

In context to the neurological system, the function and evolution of host physiology as influenced by intestinal microbiota are of great interest. It has long been understood how crucial the gut-brain axis is in controlling reactions to stress. More recently, the microbiota has become a crucial component in this gut-brain regulation, particularly under stressful circumstances brought on by actual or perceived homeostatic strain. The gut microbiota seems to have an impact on the growth of emotional behavior, stress- and pain-modulation systems, and brain neurotransmitter systems, according to studies employing mice raised in a germ-free environment. Current evidence suggests that multiple mechanisms, including neural pathways and immune signaling, may be involved in gut microbiota–to–brain signaling and that the brain can in turn alter microbial composition and behavior via the autonomic nervous system. The gut microbiota has been implicated in a variety of stress-related conditions including anxiety, depression, and irritable bowel syndrome, although this is largely based on animal studies or correlative analysis in patient populations. Additional research in humans is sorely needed to reveal the relative impact and causal contribution of the microbiome to stress-related disorders. We will briefly explore the crucial aspect of this axis in

this review, as well as the methodological issues that have been raised in previous attempts to define normal microbiota and chronicle its temporal development.

Keywords- Microbiome, Gut-Brain axis, Stress, Neural and immune pathway.

1. Introduction

A gamut of environmental entanglements is persisting in this 21st century [1, 2, 3, 4]. At the neurological, hormonal, and immunological levels, the gastrointestinal system and the brain communicate in both directions. The brain-gut axis is a concept that is essential for preserving homeostasis [5]. The bacterial microbes that reside within the human system have a symbiotic relationship with us, with a significant population living in our gastrointestinal tract [6, 7]. Current developments in sequencing technology have shown that the microbiota within the human stomach contains approximately 40000 bacterial species of 1800 different phyla. Even babies born by cesarean section have a different microbiota composition as compared with vaginally delivered newborn infants [8].

In this review, we will briefly go over the key elements of this axis as well as the methodological issues that have been raised to define normal microbiota and track its temporal evolution [9]. With reference to the previously understood roles of the microbiota as well as an assessment of exciting new data suggesting a role for the microbiota in the modulation of mood and behavior, we examine the methods that have been used to clarify the impact of the enteric microflora on this axis and vice versa. The evidence in favor of the microbiota's involvement in disease states is examined along with mechanistic insights that are offered [10].

2. Gut Microbiome

The human gut microbiome is the combined genetic material of the microorganisms in the gut. The gut is home to trillions of different

microorganisms, mostly bacteria but also yeasts, viruses, helminth parasites, and protozoa [11]. Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia phyla are present in relatively low abundance, and these two dominating phylotypes, Bacteroidetes and Firmicutes, largely define the bacterial gut microbiome. Healthy adult humans each typically harbor more than 1000 species of bacteria belonging to relatively few known bacterial phyla with Bacteroidetes and Firmicutes being the dominant phyla [12].

Despite a recently reduced revision to the ratio of microbial to human cells, it is clear that the former outnumbers the latter. According to previously reported studies, the weight of the human brain is comparable to the overall weight of these gut microorganisms, which is 1-2 kg [13]. Mammals have never existed without bacteria, except for laboratory conditions, because microbiota and their host organisms co-evolved and are mutually required for survival [14].

The host's digestion and nutrition depend heavily on the gut microbiota, which can produce nutrients from substrates that the host would otherwise be unable to digest. The host immune system and the microbiota interact in a wide variety of intricate and reciprocal ways [15]. The microbiota is crucial to educating the immune system to operate effectively, as the immune system needs to learn to accept the commensal microbiota and react to infections appropriately. Based on research demonstrating the microbial conversion of dietary phosphatidylcholine into the proatherosclerotic metabolite trimethylamine-N-oxide (TMAO), there is growing interest in a connection between microbiota and cardiovascular disease [16]. As we learn more about how the microbiota can affect the host, it is intriguing to speculate that intestinal microbiota may result in

disease. However, it is also noted that the diseased state can lead to changes in the microbiota through a variety of mechanisms, including changes in eating habits and bowel function as well as the addition of medications like antibiotics [17].

2.1 Gut Microbiome and stress-related behavior

Genetic and environmental factors, particularly early-life exposures, have been linked to individual variability in life-long stress response and vulnerability to stress-related diseases may change how central brain networks are created and function during development. It is interesting to note that it's progressively becoming more evident that bacteria are necessary for appropriate brain growth [18].

Animal studies have provided much of the evidence that the microbiota plays a critical role in controlling physiology, behavior, and brain function alterations brought on by stress. In 2004, it was discovered that GF mice had a heightened HPA axis response to stress, which could be corrected by colonization with a particular species of Bifidobacteria. The findings of subsequent studies have maintained the link between gut microbiota and stress responsiveness, with reports that stress exposure during adolescence or adulthood can alter the microbiota composition of an organism and that microbial populations can influence an organism's stress responsiveness [19].

An interesting recent report demonstrated that the intake of a probiotic-rich fermented milk product resulted in alterations in brain activity in response to visual emotional stimuli as measured by functional magnetic resonance imaging as compared to the intake of a control product [20]. The hypothalamic-pituitary-adrenal (HPA) axis is activated by both psychological and physical stimuli. This causes several hormonal reactions, such as the release of corticotropin-releasing hormone, which subsequently triggers the

release of corticotropin throughout the body, stimulating the production of glucocorticoids (cortisol) in the adrenal cortex. In addition, after experiencing physical and mental stress, catecholamines (adrenaline and noradrenaline) are released. The gut microbiota and, more recently, the GI tract is both responsive to stress and its mediators [21].

3. Gut-Brain Axis

The gut-brain axis idea has been understood for some time, and it has been applied as a framework to evaluate the methods by which these two systems communicate in both directions. The term "microbiota-gut-brain axis" is increasingly used to describe the expansion of this axis to cover the contents of the intestinal lumen [22]. With roughly 50,000 extrinsic and 100 million intrinsic sensory afferent neurons, the human gut is densely innervated. These neurons all work in close proximity to the trillions of microorganisms that are housed in the intestinal lumen. It suggests that neural pathways play a crucial part in the communication between the bacteria in the stomach and the brain [23].

Immune, endocrine, humoral, and neurological connections between the central nervous system and the gastrointestinal tract enable bidirectional communication. Additional studies indicated that the brain's ability to function is influenced by the release of cytokines, neurotransmitters, neuropeptides, chemokines, endocrine messengers, and microbial metabolites like "short-chain fatty acids, branched-chain amino acids, and peptidoglycans" from the gut microorganisms [24]. After then, the intestinal microbiota can direct these substances to the brain via the blood, neuropod cells, neurons, endocrine cells, and possibly more. The products then reach critical brain regions, where they have an impact on several metabolic procedures. A major node in the gut-brain behavioral

network, studies have demonstrated the connection between the hippocampus, the prefrontal cortex, and the amygdala (responsible for emotions and motivation).

4. Mechanism of communication between Gut microbiota and brain

The specific function of the microbiome in gut-brain-gut signaling pathways is yet unknown. obstructing our efforts is the current state of our incomplete understanding of the identification and purpose of the complex and diverse microbial population that makes up the gut [25]. Yet, developments in the metagenomics field promise to allay this worry. Between the gut and the central nervous system (CNS), there is a complex network of communication that includes the enteric nervous system (ENS), sympathetic and parasympathetic branches of the ANS, neuroendocrine signaling pathways, and neuroimmune systems.

The thoracic and upper lumbar spinal cord, as well as the nucleus of the solitary tract in the caudal brainstem, receive visceral feedback from the gut via afferent spinal and vagal sensory neurons, which activate polysynaptic inputs to higher brain regions like the hypothalamus and limbic forebrain [26]. Many theories regarding how the intestinal communal microflora may affect ENS and CNS signaling, including neurological and humoral pathways as well as direct and indirect modes of action, have been put forth [27].

4.1 Neural Pathway

The ENS, a complex peripheral neuronal circuit made up of sensory neurons, motor neurons, and interneurons that is implanted inside the gut wall innervates the gut. Although the ENS is capable of basic GI (gastrointestinal) functions, such as motility, mucous secretion, and blood flow, are independently regulated, vagal and to a lesser extent spinal motor inputs provide central control of gut functions, which serve to synchronize gut functions with the overall

homeostatic state of the organism. This centralized control over the ENS is crucial for adaptive gut reactions during stressful situations that indicate a threat to the organism's homeostasis. According to some theories, the Vagus nerve is the most crucial neural pathway for the bidirectional communication between the brain and gut microbes [28].

In recent experiments, chronic administration of Lactobacillus rhamnosus (JB-1) altered the expression of central GABA receptors in a region-dependent manner. This lowered anxiety and depressive symptoms as well as the stress-induced corticosterone response was also attenuated [29].

4.2 Immune Signalling

The dynamic equilibrium between the brain and the gut is mediated in significant part by the immune system. The HPA axis, ANS, and ENS all have direct interactions with the immune system, and the gut is a key immunological organ that serves as a crucial barrier against pathogens derived from the external world and the internal biological environment. The stimulation of immunological signaling pathways from the body to the brain by pathogenic microbes affects behavioral measurements, according to research utilizing animal models [30]. Although the molecular basis of gut microorganisms' contributions to the maturation and strengthening of the immune response are understood, most are still unclear. It has been suggested that probiotic microbes' immunoregulatory benefits result from the expansion of T-regulatory cell populations and the production and secretion of the anti-inflammatory cytokine IL-10 [31].

By binding to toll-like receptors (TLRs), such as TLR-4, which are expressed on monocytes, macrophages, and microglia, the lipopolysaccharide (LPS) component of gram-negative bacteria's cell walls can trigger the release of pro-inflammatory

cytokines like interleukin (IL)-6 and IL-1b [32]. It is believed that intestinal permeability breaks down in disorders including irritable bowel syndrome (IBS) and depression, which allows germs to move from the gut lumen to the systemic circulation where they can trigger TLR-4 on circulating immune cells to cause an inflammatory response. The inflammatory response in the gut can also signal to the brain via the vagus nerve [33].

Using a probiotic that included several Lactobacilli, Bifidobacteri, and Streptococcus species, researchers were able to reduce systemic inflammation and the symptoms of illness brought on by bile duct ligation. Probiotics improve inflammation-associated sickness behavior by altering communication between the peripheral immune system and the brain. These studies show that the gut microbiota can control the peripheral inflammatory response, which can impact mental health and behavior [34].

5. Stress-Related Disorders

5.1 Irritable bowel syndrome (IBS)

IBS is thought to represent pathologically disturbed homeostasis of the gut-brain axis. This illness is strongly associated with anxiety and depression and is linked to changed bowel habits and visceral abdominal pain [35].

Many IBS symptoms and comorbidities have probable explanations in abnormalities in the processing of interoceptive signals from the gut (visceral hypersensitivity) and other bodily regions (esophagus, stomach, urine bladder, and muscle). The findings are most compatible with changes in endogenous pain modulation systems at all levels of the GB axis, in particular the spinal cord, brainstem, and insular cortex. However, the mechanisms behind the distinctive hypersensitivity are still poorly understood [36].

IBS has been linked to aberrant serotonin/5-hydroxytryptamine (5-HT) metabolism, dysregulated brain-gut axis, and

increased mucosal nerve fiber or neurite densities in the intestines. The symptoms of IBS were related to several 5-HT receptor subtypes, including 5-HT3, 5-HT4, and 5-HT7 receptors [37]. IBS patients' colons were shown to have high concentrations of mucosal nerve fibers that express the 5-HT7 receptor. In mice models of visceral hypersensitivity, the 5-HT7 receptor's function in intestine hyperalgesia was shown, and intestinal pain levels were decreased by a new 5-HT7 receptor antagonist given intravenously. 5-HT_7 receptor-dependent intestinal neurite outgrowth contributes to visceral hypersensitivity in irritable bowel syndrome [38].

The goal of IBS treatment is to reduce symptoms, and it can be quite successful. It might also involve psychotherapy, probiotics, medicine, and dietary adjustments. Increasing soluble fiber intake is one dietary approach, as is eating a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) [39]. The "low FODMAP" diet is not meant to be used as a lifelong therapy; rather, it is intended for short- to medium-term use. Loperamide, a medicine, can aid with diarrhea, whilst laxatives can help with constipation. Antidepressants can be utilized even in patients without a concomitant mood illness, frequently in doses that are lower than those used for depression or anxiety [40].

5.2 Major Depressive Disorder (MDD)

One of the main theories put up to explain a gut-brain connection in stress-related diseases is that the "leaky gut" phenomenon, which leads to MDD, is caused by disturbed gut barrier function. According to the theorized mechanism of action, stress on the mind or body weakens the GI tract's epithelial barrier, increasing intestinal permeability and allowing gram-negative bacteria to pass the mucosal lining and enter immune cells and the ENS. This leads to the activation of an immune response characterized by increased

production of inflammatory mediators such as IL-6 and IFN γ [41]. Animal models have improved our understanding of how the gut microbiota may influence stress-related disorders, including depressive-like behaviors. Maternal separation is frequently used as a model of early life stress that provokes an adult depressive and anxiety-like phenotype, along with alterations in monoamine turnover, immune function, and HPA axis activation.

Probiotics and prebiotics have been shown to have positive effects on healthy people, despite the fact that clinical research has not yet shown whether they are effective in treating MDD [42].

6. Conclusion and Future directions

The Human Microbiome Project, MetaHIT, the American Gut Project, the British Gut Project, as well as significant gut microbiome cohort analyses, are currently ongoing large collaborative projects that have been crucial in studying and defining the gut microbiota at a population level**.** It is hoped that during the coming years, the processes underlying the advantageous benefits of particular bacterial strains will become clear. It is urgently necessary to have a better knowledge of the developmental effects of microbiome alterations on behaviors associated with stress and cognitive problems. Finally, more investments in extensive clinical trials are required to ascertain the effectiveness of psychobiotic-based therapies for illnesses associated with stress. Furthermore, the connection between nutrition and the microbiota-gut-brain axis is ready to be explored in order to create therapeutic approaches for treating illnesses associated with stress. The gut microbiome has been linked to a causal relationship with metabolic traits, with increased gut butyrate production associated with improved insulin response following an oral glucose tolerance test but errors in production or absorption of propionate causally linked to increased risk

of type II diabetes, according to the most current combination analysis using GWAS of the microbiome and metagenomic sequencing [43, 44]. Future research on the topic is anticipated to benefit from emerging technologies, such as whole-genome shotgun metagenomics, which offer greater sensitivity and resolution for microbiome investigation. Optimization of the various process parameters can also be a promising future scope in this domain [45, 46]. The assay of various enzymatic activities may also be evaluated for enhancing the process output [47].

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