Brain–Gut–Microbiome Axis

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Beginning with the concept of the brain–gut axis, the importance of the interaction between the brain and the gastrointestinal tract has been extended to the microbiome with increasing clinical applications. With the recent development of various techniques for microbiome analysis, the number of relevant preclinical and clinical studies on animals and human subjects has rapidly increased. Various psychotic symptoms a ect the intestinal microbiome through the hypothalamus–pituitary–adrenal gland axis. Conversely, the intestinal microbiome regulates the gastrointestinal tract environment and affects psychological factors by means of the microorganisms or their metabolites, either acting directly on the brain or through the synthesis of various neurotransmitters.

Keywords: brain–gut axis ; microbiome ; psychiatry ; neurotransmitters

1. Introduction

The connection between the brain and gut is known to affect human emotion, motivation, and higher cognitive function, in addition to maintaining homeostasis of the gastrointestinal tract. This complex interaction is referred to as the brain–gut axis (BGA). It coordinates and integrates gastrointestinal function in addition to connecting the brain to peripheral functions [1]. During these processes, mechanisms such as immune response activation, preservation of intestinal permeability, various intestinal responses, and gastrointestinal tract–endocrine signaling occur [2]. Therefore, it can be inferred that signaling between the brain and gastrointestinal tract is based on regulating the neuro-immuno-endocrine system. Such bidirectional signaling systems include the central nervous system (CNS), autonomic nervous system, gastrointestinal nervous system, and hypothalamic–pituitary–adrenal (HPA) axis. The autonomic nervous system, which includes sympathetic and parasympathetic nerves, starts in the lumen of the intestinal canal and reaches the CNS through the enteric, spinal, and vagal pathways. It sends signals from the brain to the intestinal canal and vice versa [3].

The HPA axis is the most critical system for coordinating adaptive responses to various stressors. As a part of the limbic system, it is essential for regulating brain functions, including memory and emotional responses [4]. When the HPA axis is activated due to environmental stress or an increase in proinflammatory cytokines, corticotropin-releasing factor (CRF) is secreted from the hypothalamus, stimulating the secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland. As a result, cortisol—one of the major stress hormones that affects various parts of the human body including the brain—is secreted from the adrenal cortex. Therefore, the brain can coordinate the function of the gastrointestinal tract via the integration of signaling through nerves and hormones.

2. Neurotransmitters in Microbiomes

Metabolites produced by gut microbiota can affect the brain–gut axis. Butyrate, a well-known short-chain fatty acid (SCFA), is synthesized by microbiota and inhibits histone deacetylases to promote memory and neural plasticity [5]. In particular, propionate produced by microbiota protects the blood–brain barrier (BBB) from oxidative stress [6]. SCFAs influence neuroinflammation by coordinating the proliferation and recruitment of immune cells, such as T-cells and neutrophils, as well as inflammatory cytokine production.

In addition to SCFAs, various microbiota-derived metabolites act as essential neuroactive molecules in the central nervous system (CNS). Lactobacillus spp. and Bifidobacterium spp. synthesize neurotransmitters, such as acetylcholine and gamma-amino butyrate (GABA), while Streptococcus spp., Enterococcus spp., and Escherichia spp. synthesize serotonin, dopamine, and norepinephrine [7][8]. However, it has not been clearly identified how neurotransmitters synthesized by microbiota work within the host. Some essential vitamins—such as vitamins K, B2, B9, and B12, synthesized by microbiota—have a neuroprotective effect on the CNS [9]. Previous studies have reported how microbiota regulate the bioavailability of various substances necessary for neurotransmitter synthesis [10][11]. Gut microbes can metabolize the essential amino acid tryptophan as a precursor for the synthesis of indole, serotonin, and melatonin, thereby limiting the availability of tryptophan for the host [12]. Pseudomonas spp. synthesizes serotonin from tryptophan and is used for toxicity and intercellular signaling. Therefore, the gut microbiota-associated decrease in circulating

tryptophan affects serotonergic transmission and function of the CNS and enteric nervous system, and tryptophan metabolism induced by microbiota affects tryptamine production through the action of tryptophan decarboxylase [13]. Tryptamine modulates the inhibitory response of cells to serotonin by enhancing serotonin secretion from enterochromaffin cells [14]. Gut microbiota-associated tryptophan metabolism yields a number of substances affecting the brain and behavior including kynurenine, quinolinate, indole, and indole derivatives [15]. Kynurenine and quinolinate can affect brain function, leading to depressive symptoms and host tryptophan deficiency [16]. The production of kynurenine and quinolinate reduces tryptophan concentration in the blood and inhibits the production of major neurotransmitters, such as serotonin, in the brain [17]. In addition, indole and indole derivatives, including indole acetic acid (IAA) and indole propionic acid (IPA), alter CNS metabolism [18]. Therefore, tryptophan catabolism associated with microbiota is the most important regulator of the brain–gut axis.

Dopamine is the most important neurotransmitter that coordinates reward-based motivation and plays a precursor role in synthesizing catecholamines, such as norepinephrine and epinephrine. To date, the functions of norepinephrine include arousal and alertness in sensory signal detection and the waking state. In recent studies, it was reported to play an important role in cognitive functions, such as behavior, memory, learning, and concentration [19]. Various microbes are involved in catecholamine synthesis and function. The growth rate of pathogenic Escherichia coli 0157:H7 (EHEC) increased in the presence of dopamine and, in particular, norepinephrine, as enhanced motility, biofilm formation, and virulence were observed [20]. The growth of Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, Shigella sonnei, and Staphylococcus aureus also increased in the presence of norepinephrine [21]. E. coli, Proteus vulgaris, Serratia marcescens, Bacillus subtilis, and Bacillus mycoides acted as harbors of relatively high levels of norepinephrine with regard to biomass [22]. The role of the microbiota in coordinating norepinephrine and dopamine levels in vivo has not yet been confirmed, but it appears to be involved in their biosynthesis/catabolism within the host. In a recent study, the concentration of norepinephrine in the cecal lumen and tissue of GF animals was significantly lower, and the cecal level of norepinephrine recovered when a mixture of microbiota and 46 clostridia species was colonized [23]. These studies suggested that microbiota affect norepinephrine in the lumen, but it is unclear whether the bacteria directly produce norepinephrine or coordinate its production by the host. The effect of microbiota on the catecholamine system is functionally important, and the behavioral response to cocaine increased in microbiota-deficient mice, which may be associated with the increased activity of the D1 dopamine receptor Drd1 and GluR2 AMPA receptor Gria2 [24]. The behavioral response to cocaine normalized when animals that received antibiotics were also supplemented with SCFA or microbial fermentation byproducts, which suggests that the microbiota has an indirect effect on reward behavior.

Gamma-aminobutyric acid (GABA) is an important inhibitory neurotransmitter in the CNS, and its receptors are widely distributed. GABAergic neurotransmission is important for various CNS functions, such as behavior, pain, and sleep, as well as gastrointestinal tract functions, such as intestinal motility, gastric emptying, nociception, and acid secretion [25]. Microbes consume or produce GABA. In terms of consumption, the GABA shunt, which converts GABA to succinate through the TCA cycle, is important. E. coli produces GABA from sole carbon and nitrogen sources, but the general function of GABA-consuming microbiota remains unknown. In contrast, the systemic function of GABA has been well described, and various types of microbes are known to synthesize GABA. Unlike other neurotransmitters, GABA production has been studied extensively in terms of physiology, and GABA secretion plays a role in reducing the intracellular pH of the glutamate acid resistance system [26]. The microbiota affects circulating GABA levels, and significant decreases in luminal serum levels have been reported in GF animals [27]. Members of the Bifidobacterium and Lactobacillus genera are involved in GABA synthesis, and when Lactobacillus rhamnosus (JB-1), the most frequently reported one, was injected into mice, depressive symptoms and anxiety decreased in association with the activity of the vagus nerve, and changes in cerebral GABAergic activity were observed [28]. In a recent study, oral administration of Bifidobacterium breve NCIMB8807 pESHgadB in a rat model reduced GABA synthesis and sensitivity to visceral pain through the overexpression of glutamate decarboxylase B [29]. There are only a few, similar preliminary studies on this in humans, but tuning the human microbiota is expected to affect GABA levels. Dietary regulation changes the function and composition of the microbiota, and the ketogenic diet is associated with increased levels of GABA in cerebrospinal fluid and symptom improvement in children with treatment-resistant epilepsy [30]. In a recent fecal transplant study, GABA was the most variable metabolite in obese patients who received fecal transplants from lean donors, and this was also associated with improved insulin sensitivity [31].

3. Conclusions

With the development of techniques for analyzing the human gut microflora, the importance of the microbiome for physical and mental health is increasingly acknowledged. The human brain and gut interact through the brain–gut axis. Psychosocial or psychological stress leads to cortisol secretion through the HPA gland axis, and this hormone changes intestinal permeability and the environment of gut microbes. In addition, the activation of the autonomic nervous system is

associated with changes in gastrointestinal motility and the synthesis of various neurotransmitters. Conversely, dysbiosis of microorganisms in the gastrointestinal tract increases intestinal permeability, and various metabolites and inflammatory substances reach the brain through circulation, resulting in psychological symptoms such as depression, anxiety, cognitive decline, and a lack of social functioning. In particular, the activation of the immune response due to changes in the intestinal microflora causes the secretion of various inflammatory cytokines, which reach the brain, affecting psychological functions. Therefore, the brain–gut microbiome axis should be investigated as a bidirectional pathway, rather than emphasizing on the importance of either direction. In addition, the microbiome is known to produce or participate in the synthesis of various neurotransmitters and neuromodulators. However, most studies have been preclinical, and more human studies need to be conducted based on the results of animal studies. Increasing attention is being paid to treatment-resistant depression and treatment-resistant psychosis, for which it is difficult to achieve therapeutic benefits due to patients' limited response to psychotherapy and psychiatric drugs. Further, the treatment of psychological disorders and the improvement of psychological symptoms by researching microbiomes may bring about innovative changes in clinical practice in the future.

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