The influence of the gut microbiota on the nervous system

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Abstract: Gut microbiota is trillions of bacteria that dwell in the gut and are closely related to human health by precipitating various signals to the human brain. Even some slight deviations from the standard metabolic value of substances production or intake will result in mental issues, which has aroused concerns around the world for a while. There are three main pathways facilitate transporting information between the gastrointestinal tract and the nervous system: the autonomic nervous system(ANS), hypothalamic-pituitary-adrenal(HPA)axis, and the immune system. Mice experiments have proved the relationship between intestinal flora and people's mental state as several types of neurotransmitter and microbial metabolites have a direct impact on brain secreta balance, therefore stimulating neurological disorders. However, statistics based on human and clinical studies have not been sufficient to demonstrate how the gut microbiota contributes to metabolic disturbances in the brain. In this review article, we systematically describe the mechanisms between the three pathways and the chemicals that produce the pathological effects, focusing on the pathogenesis of anxiety and depression. There is still great uncertainty about whether daily food intake protects against certain neurological disorders. In the future, it is still necessary to study how to intervene the intestinal nerve axis in order to prevent and treat diseases such as anxiety and depression.

1. Introduction

According to government data from many countries, the incidence of neurological diseases is increasing year by year. Until 2021, the global pooled prevalence of depression, anxiety, and distress was 31.4%, 31.9%, and 37.9%, respectively [1]. In the last few years more and more scientists discovered and proved the relationship between intestinal microbe and neurological diseases, which is helpful for people to further cure the disease of neurological diseases.

The gut microbiota - the trillions of bacteria that dwell in the gastrointestinal tract - has been found to not exclusively be a fundamental part of insusceptible and metabolic wellbeing, yet additionally appears to impact improvement and infections of the intestinal and focal sensory system, including motility disorders, behavioral disorders, neurodegenerative disease, cerebrovascular accidents, and neuroimmune-mediated disorders [2]. Neurological diseases, such as Alzheimer's disease, are conditions that affect the brain as well as the nerves present throughout the human body including the spinal cord. A few different pathways of communicating between the gastrointestinal tract and the nervous system have been discovered along the "gut-brain axis", such as those controlled by the autonomic nervous system (ANS), hypothalamic-pituitary-adrenal (HPA) axis, and the immune system [2,3]. One potential mechanism is that microbial metabolites produced in the gut take the role of synthesizing neurotransmitters and modulating various indexes. B. Infantis, for example, has been shown to boost plasma tryptophan levels, influencing brain transmission. 5-HT [4]. Relevant studies have proved that specific gut microbiota can influence the physiology and neurochemistry state of the central nervous system (CNS). For example, germ-free mice that lack associated microflora exhibit neurological deficiencies in learning, memory, recognition, and emotional behaviors [3]. By studying

animal models, evidence of mutual effects can be traced between GI pathology and neuropsychiatric conditions and therefore deduce the incidence of anxiety, depression, and irritable bowel syndrome.

In this review article, we spotlight on the impact that the intestinal microbiome leaves on the nervous system and the basic mechanism behind such a relationship——the three main pathways connecting gut and brain. Furthermore, we will discuss the pathological effects of gut microbial metabolites on relevant neurological diseases such as anxiety and depression. We will extend to possible mental therapies based on recent findings in gut-and-brain mechanisms to prevent initiate of such diseases due to gut microbiota. However, we admit that not enough statistical support is presented to consolidate such a relationship in humans firmly and further research is required to explore this pattern.

2. Intestinal microbiome affects the nervous system

The central nervous system (CNS), gut, and gut microbes together form a bidirectional information transmission pathway between brain and gut, which is named the microbial-gut-brain axis. In other words, microbes and their metabolites present in the gut participate in the regulation of the CNS through this axis. There are many ways of action in this pathway, among which three are the most important, the ANS, hypothalamic-pituitary-adrenal (HPA) axis, and the immune system.

2.1 Autonomic nervous system (ANS)

The Nervous system is divided into CNS and peripheral nervous system (PNS). PNS is the nerve emanating from the CNS and distributed throughout the body [5]. ANS is a part of the peripheral nervous system, which can innervate the internal organs. Inside the gut lies the enteric nervous system (ENS). ANS and the internal nervous system are positioned in the digestive tract's wall. Signals from the gut move first through the internal nervous system, then to the ANS, and finally to the CNS.

The vagus nerve plays a significant role in signaling in the intestinal tract. It is a mixed nerve. 80% of the vagus are afferent fibers and 20% are efferent fibers. vagal afferent fibers are distributed in all layers of the digestive wall, but do not pass through the upper cortex, so they can not come into contact directly with the gut microbiota [6]. As a result, these fibers can only detect microbiome signals indirectly, either via the diffusion of bacterial chemicals or metabolites, or via the transmission of cavity signals by other epithelial cells. The ANS is also filled with vagus nerves. So, when the vagus nerve recognizes a signal from the gut, that signal travels through the vagus nerve, through the ANS to the CNS, and back to the brain. Intestinal endocrine cells directly activate 5-HT3 receptors which are sited on vagal afferent fibers by releasing serotonin (5-hydroxytryptamine, 5-HT) [7]. Or intestinal hormones (such as cholecystokinin and glucagon-like peptide-1, peptide YY) targes the brain through vagal afferent nerves. These afferents express receptors for this anorexia or appetite (auxin releasing peptide, orexin) hormones. The transmission of these signals will bring some different feelings to people, such as anorexia.

2.2 Hypothalamic-pituitary-adrenal (HPA) axis

The Hypothalamic-pituitary-adrenal (HPA) axis is a complicated neuroendocrine system that includes the hypothalamus, pituitary gland (a pear-shaped organ below the hypothalamus), and adrenal gland. It governs several body systems, including digestion, the immune system, mood, libido, and energy consumption, as well as the stress response. Cortisol plays an important role in regulating stress in the body.

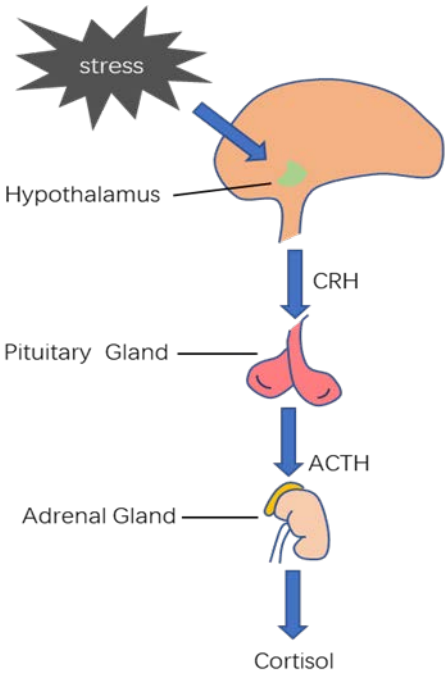

Figure 1. The pathway of stress affects the HPA axis [9].

When chronic stressors are sensed, (Figure 1) the hypothalamus releases corticotropin-releasing factor (CRH) and sends it through the bloodstream to the pituitary gland, which then can produce adrenocorticotropic hormone (ACTH). This is carried through the blood to the adrenal glands. The adrenal cortex produces corticosteroids, the most important of which is cortisol. Cortisol mobilizes glucose which is deposited in the liver to provide the body with a constant supply of energy to relieve the pressure [8]. A healthy stress response is one in which cortisol levels rise rapidly in response to stress and decrease when the stress is over [9]. Because when cortisol reaches a certain level, it triggers negative feedback to the hypothalamus to inhibit the release of this hormone, which then releases CRH. Cortisol also inhibits the release of this hormone by inhibiting the anterior pituitary gland, which releases ACTH. This causes the stress response to shut down because homeostasis has been restored. These negative feedback loops are designed to keep the body safe from prolonged HPA activity [9].

Now, a growing body of research suggests that HPA axis overstimulation and high cortisol levels are associated with mood disorders like anxiety, depression. There have also been studies showing that gut microbes affect brain function and neurogenesis, including sensitivity to stress [10]. Aadil Bharwani et al. [11], studying the effects of chronic social stress on the microbiome, found that intestinal microbiome richness and diversity were reduced in mice exposed to chronic stress. And the results of C. Heim et al. [12] showed that people without major depression showed lower baseline and stimulated plasma cortisol concentrations than people with major depression. And it has been shown that chronic stress increases baseline cortisol levels. This means that the body's response to acute stress is weakened, and stress-induced cortisol levels take longer to return to pre-stress levels [13].

2.3 Immune system

Because the gut connects the internal and external environments of the body [14, 15], the gastrointestinal tract (GIT) is closely related to and in constant communication with the immune system. Gut bacteria thus develop and regulate the host's immune system, which likewise influences the composition of the gut microbiome [16], which is a particularly reciprocal mechanism. The host immune system is not only responsible for ensuring the normal growth of beneficial microbiota in the gut and preventing the overgrowth of specific bacteria, but also generates a corresponding body response when the gut barrier encounters pathogenic bacteria or molecules [16]. Microbes also regulate the immune system and pathogens, and these gut microbes can interact directly with pathogens or indirectly stimulate the immune system to respond to pathogens. Alterations in the gut microbial

community, which affect changes in gene expression and monoamine levels, may be mediated by changes in short-chain fatty acids (SCFA), which regulate microglial function in the CNS. The immune system thus maintains gut homeostasis by establishing an appropriate balance between tolerance to symbiotically harmless, symbiotically beneficial, and opportunistic pathogenic bacteria. A solid and ideal balance is achieved when the immune system can communicate properly with the gut microbiome, and a healthy gut barrier, along with a normal gut microbiome, is key to interfering with the process.

The CNS is closely linked to the immune system due to nerve fiber mediation, and these nerve fibers also change as they descend from the brain to primary and secondary lymphoid tissues [17]. These nerves and immune cells are directly affected by these substances. Another pathway that regulates immune system function is due to the body's production of neurohormones in the hypothalamus, which in turn induces the body to produce a further series of neuroactive compounds. Vice-versa, cytokines are produced by immune cells and can saturate the transport system through the blood circulation to cross the blood-brain barrier, The CNS function is thus greatly affected. The defense of the central nervous system is depending on blood-brain barrier, which plays a decisive role in it, as it may negatively affect neuronal activity by restricting access to various substances and cells [18].

Corresponding receptors for many neurotransmitters and neuropeptides, such as acetylcholine, epinephrine, beta-endorphin, neuromodulin U, substance P, neurotensin, and vasoactive intestinal peptide, are present in different types of expressed in immune cells. Neuropeptides and neurotransmitters are synthesized and released from nerve endings and inflammatory immune cells. They play an interfering role in the nervous and immune systems, and they are really important to infection in the immune response by microorganisms and allergic immunity [19].

Numerous forms are manifested in brain inflammation, including microglial and T-cell responses as well as humoral responses, including antibody production and complement-mediated processes. Most resident immune cells in the brain are microglia, which make up approximately 5-20% of glial cells [20]. Yolk sac erythrocyte myeloid progenitors can differentiate into microglia [20]. Microglia play several roles from phagocytosis to antigen presentation to cytokine production to activation of inflammatory responses, [20,21] that are typical of myeloid cells Features. Microglia possess a wide range of cellular processes capable of rapid clearance of debris and infectious agents and immunosurveillance, estimated to take 2-5 hours to survey the entire brain, but with a very limited range of physical motion [21,22]. Microglia have a very broad range of activation states, ranging from pro-inflammatory to tissue-protective [23,24]. During neural development, microglia mark and clear synapses for pruning purposes Promotes neuronal circuit wiring and produces cytokines and chemokines that can direct neuronal differentiation [20,24]. A variety of inflammatory mediators (such as pro-inflammatory cytokines, prostaglandins, reactive oxygen species, etc.) can be secreted by microglia [25]. During CNS injury or disease, microglia are activated and initiate immune responses to accelerate tissue repair and restore normal physiology.

3. Anxiety

Dysbiosis and the inflammation it produces have been linked to a variety of mental illnesses, including anxiety and depression, which are prevalent in today's society. Among them for the generation of anxiety, the current research shows that there are many reasons for its generation. Gut microbes can cause anxiety disorders by the ANS, the HPA axis, and the immune system, respectively.

3.1 Autonomic nervous system (ANS)

Anxiety disorders caused by the ANS are mainly related to gamma-aminobutyric acid which also is called GABA. GABA is produced by lactobacillus and bifidobacterial in the gut. The main synthesis pathway of intestinal GABA is synthesized by L-glutamate decarboxylase using substrate glutamate. It is an inhibitory neurotransmitter that acts on nerves in the brain and spinal cord, modulating and blocking impulses between nerve cells by binding to receptors on neurons (GABA-A and GABA-B)

[26]. It plays a main role in people's mental adjustment. If a person's body does not have a certain concentration of GABA, the information in the brain has been abnormally active transmission, will produce anxiety, serious can lead to anxiety disorder, personality disorder [26].

When GABA is released into postsynaptic nerve terminals, GABA receptors are activated. In the CNS, they are thought to be significant inhibitory receptors. GABA receptors are classified as GABA-A or GABA-B receptors.

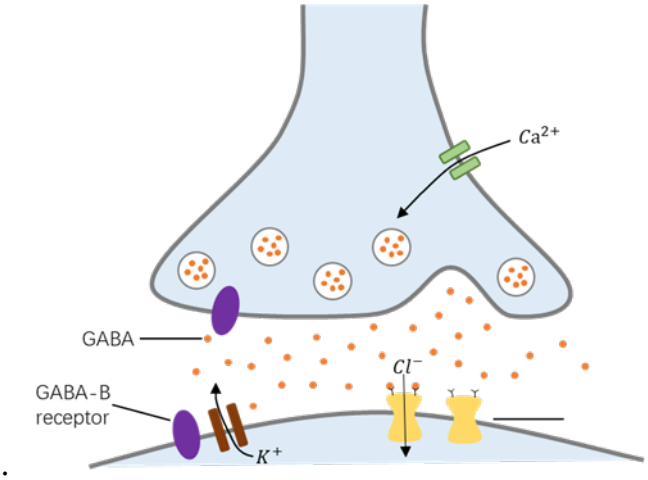

Figure 2. Two kinds of GABA receptors on neurons [26].

GABA-A is a ligand-gated ion channel/inotropic type of receptor. GABA-A is considered to be rapid synaptic inhibition which is a cylindrical receptor assembly [27]. GABA-A receptor is composed mainly of nineteen subunits. The main synapse isomers include two α1 subunits, two β2 subunits, and one γ2 subunit and the five receptor subunits are assembled pseudo-symmetrically around the extracellular vestibule and intact ion channels [27]. The subunits surrounding the pentamer ring are arranged in a counterclockwise direction, while GABA binds to each of the classical neurotransmitter sites in the β2-α1 interface. So, one GABA-A receptor binds to two GABA receptors every time. The role of GABA is to reduce the excitability of neurons through neurotransmission. After GABA is produced in the gut, it is recognized by receptors in the gut and enters the intestinal nervous system, where it is transmitted between neurons and affects nerve impulses [28]. When GABA is transmitted in the neuron and reaches the presynaptic terminal (when the action potential invades the nerve terminal), the calcium channel located at the presynaptic terminal opens, resulting in an instantaneous increase in local calcium concentration in the presynaptic active region [28]. Calcium ions trigger exocytosis of synaptic vesicles, which allows the neurotransmitters contained in the vesicles to enter the intercellular space. In the intercellular space, two molecules of GABA can bind to two binding sites on the surface of the GABA-A receptor which locates on the postsynaptic membrane (Figure 2). The effect is to open GABA-A receptor channels through which chloride ions enter the cell. Since chlorine ions are negatively charged, they reduce the resting potential of the cell and make it harder to generate an action potential.

When GABA in the body is insufficient, it is difficult to occur the above mechanism of an action to reduce the production of an action potential, continuous production of action potential, will lead to anxiety, serious and even evolve into anxiety. It has also been found that lactobacillus and bifidobacterium strains of bacteria can effectively increase the concentration of GABA in ENS. In addition, a mouse study showed that Lactobacillus rhamnosus was associated with mRNA expression of GABA receptor subunits, which are associated with anxiety. In experiments, mice fed Lactobacillus rhamnosus were less anxious than control mice [29], suggesting that probiotics affect anxiety. Clinically, drugs that increase GABA levels are commonly used as anticonvulsants, sedatives, and antianxiety agents. In this category of diseases caused by reduced GABA concentration, stimulating GABA-A receptor activity is not the primary treatment because of the addictive potential and deadly side effects of such drugs. Treatment is usually performed with GABA analogs such as valproic acid.

GABA-B receptor is a kind of G protein-coupled receptor. There are GABA-B receptors in the presynaptic membrane and the postsynaptic membrane between two adjacent neurons. Both GABA-B receptors and potassium channels are indirectly coupled (figure 2). The activation of GABA receptors in the postsynaptic membrane leads to the opening of potassium channels in the postsynaptic membrane, through which potassium ions in the cell diffuse into the intercellular space [30]. The decrease of cell membrane potential inhibits nerve impulse. This is presynaptic inhibition.

At present, GABA-B receptor agonists also exist in clinical treatment. Baclofen, a widely used GABA-B agonist, is used to treat cramping muscles and relax them. And in an eight-week trial, 14 male veterans who had chronic post-traumatic stress disorder (PTSD) received baclofen monotherapy. After eight weeks, the results were significant [31]. These results suggest that baclofen treatment can effectively treat the symptoms of PTSD and concomitant depression and anxiety in patients who suffered from this disease caused by combat. Baclofen mainly increases CNS inhibition, which can act in the presynaptic and post-synaptic prominences, binding to GABA receptors, resulting in membrane hyperplasia, limiting calcium influx, inhibiting action potential production, and alleviating the symptoms of the disease. Baclofen is therefore considered the first treatment for spasms. In addition, sodium hydroxybutyrate is approved for the treatment of narcolepsy, and propofol is used to induce and maintain general anesthesia.

3.2 Hypothalamic-pituitary-adrenal (HPA) axis

The HPA axis is a complex system that regulates physiological homeostasis through neuroendocrine pathways and feedback loops. It's implicated in the neurobiology of anxiety, bipolar disorder, insomnia, post-traumatic stress disorder, severe depression, and other mood and functioning disorders. Many components of the HPA axis are linked to the causes of anxiety.

Ran Huo et al. [32], to study hormone and hormone receptor-related behavioral changes in the HPA axis under stress, sterile mice (GF) and pathogen-free mice (SPF) were given chronic constraint stress (CRS) for 4 hours per day. After 21 days, Multiple tests showed that SPF mice showed more anxiety-like behaviors than GF mice, and there were differences in hormones and hormone receptors between the two groups. This experiment suggests that the imbalance of the HPA axis caused by long microorganisms can affect the neuroendocrine system of the brain, leading to anxiety and other behaviors. In 2019, Kuti et al. [33] used mice to study the relationship between early-life stress and adult chronic stress and gut microbiome, and found that it altered the gut microbiome and intestinal barrier dysfunction, and increased motor activity, anxiety, and neophobia in mice. In addition, a series of changes in the HPA axis due to stress result in corticosteroids crossing the blood-brain barrier (BBB) into the brain and affecting its function. Some experiments have proved that BBB permeability is related to intestinal microbiota, but the specific mechanism is still unclear [34].

3.3 Immune system

Immune cells in the human brain are mast cells. These cells are very important and are involved in the maintenance and development of the integrity and function of all tissues. The large number of mediators produced by mast cells is why they are important. The way these mediators play a role in host defense and modulate local tissue function is by focusing other immune cells to the site of injury. One of the most important neurotransmitters in the brain is histamine, which is associated with a variety of biological functions, such as anxiety and memory [35], and mast cells can produce about half of histamine. Mast cell dysfunction, including systemic mast cell activation disorders, can lead to a wide range of neurological and psychiatric disorders, namely anxiety; [36].

It is a well-known fact that malnutrition often leads to immune deficiencies such as cell-mediated responses and humoral immunity. Anorexia nervosa (AN) is a serious eating disorder that often leads to malnutrition and cachexia. Chronic food restriction may lead to gut barrier dysfunction which may lead to further disease progression and other complications including anxiety disorders. The intestinal flora composition of AN patients is very different from healthy people in terms of type and quantity [19]. Higher concentrations of the methane-producing archaea Methanobrevibacter smithii have been reported in the guts of patients with AN. High concentrations of archaea play a good role in

transforming food into a low-calorie diet. In addition, some experiments have shown that AN patients of the same age have much less total intestinal bacteria and obligate anaerobic bacteria than healthy women, including bacteria from the Clostridium sphaeroides group, the Clostridium licheniformis subgroup and the Bacteroides fragilis group [15]. Compared with the healthy control group, we can compare that AN is related to the dysbiosis of the intestinal microflora, and its biggest feature is that there are fewer microbial species and lower taxonomic differences. This dysbiosis is also associated with associated psychopathology [37]. Many AN patient, due to severe malnutrition leading to vitamin and protein deficiencies, and most AN patients are deficient in carbohydrates and fats [37], the severity and frequency of immune impairment are lower than that observed in malnutrition. Therefore, reducing food intake may seriously affect the interaction between the immune system and the CNS. Anxiety disorders may be due to impaired communication between these systems.

Major depressive disorder (MDD) occurs when people feel very depressed or feel that their daily activities do not make sense for more than 2 weeks. The exact etiology of depression is unknown, but it is closely related to the activation of the immune system [38] and the interaction in the host and the microbiota. Although immune system regulation appears to be involved in stress-related diseases, [39] the exact mechanisms remain unclear. Changes in brain function are caused by altered immune homeostasis through the immunomodulatory properties of gut bacteria and probiotics88, as well as by host-microbiota interactions, possibly through the HPA axis. To study the effects of the immune system on stress, anxiety, and depression in midgut-brain communication, the use of immunocompromised animals is essential.

4. Conclusions

Due to the fact that gut microbiota and the nervous system are so intertwined with each other, the necessity of digging deeper into their potential impact on human health is unveiled. Information is transported through three main pathways and then conducted by the brain. During this process, any abnormal phenomenon in intestinal flora can increase the probability of neurological diseases. For anxiety, there are three potential factors leading to its onset: deficiency of GABA, imbalances of the HPA, and microbial metabolites that cause dysbiosis. Excess production of corticosteroids is prone to develop depression. However, even though the possibility that the gut microbiome can cause mental problems has been proven, the lack of statistics showing such correlation in the human population and many mechanisms that some other mental diseases caused by gut microbiota remain a secret. In the future, more experimental data directly based on the human body is required to use as evidence and more attention should be paid to this field of research.

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