The Microbiome and Neurotransmitter Activity

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Research has revealed that the gut microbiota impacts human health through several mechanisms, including modulating the immune response within the intestine, production of metabolites, and through the production of short chain fatty acids and vitamins. In this paper we explore the ability of microorganisms to produce key neurotransmitters or impact their expression through cell receptors. Neurotransmitter imbalances are implicated in a variety of human illnesses including anxiety, depression, insomnia, autism, multiple sclerosis and functional gastrointestinal disorders. A new research field is emerging to develop psychobiotics. Psychobiotics consist of probiotics or the prebiotics which support probiotic growth and they have shown to have a beneficial impact on psychiatric or neurological disorders. Understanding the unique contributions of various bacterial strains to the production or expression of neurotransmitters is a key component in the development of these new therapies. The neurotransmitters explored include serotonin (SERT), gamma aminobutyric acid (GABA), melatonin, catecholamines (CATs) and histamine. The aim of this paper is to review and summarize the available literature on the inter-relationship between various microbes in the gut microbiome and neurotransmitter activity. This includes commensals, pathogens as well as probiotics. The collected information will provide a reference guide for correlating certain disease states and conditions to microbial activity and helping clinicians select appropriate commercially available probiotics supplements and foods for optimizing health associated with the particular neurotransmitters discussed in this review.

Introduction

Anxiety and depression are widely prevalent and complex mental illnesses that can have devastating effects on the quality of life of individuals, with an increased risk of suicide [1]. The overall burden of anxiety and depression exceeds other major diseases and is continuing to rise steadily [1]. Often the onset occurs from childhood and can continue throughout a person's lifetime. Traditionally, depression and anxiety have been associated with neurotransmitter modulation. There are many theories to explain the pathogenesis of depression, including neurotransmitter dysfunction, endocrine disorders, damage to neuronal plasticity and adaptability, oxidative stress, mitochondrial dysfunction, and others [2]. Recent studies show a strong association with immune activation and cytokine levels that mediate the development of depression, as evidenced by higher levels of pro-inflammatory cytokines and related mediators in patients with depression [2].

Increasing evidence suggests that the gut microbiome is involved in the pathogenesis of anxiety and depression. Gut microbiota are associated with tryptophan metabolism, neurotransmitter production, regulation of the hypothalamic-pituitary-adrenal axis (HPA) as well as the afferent input of the vagus nerve [1]. Given the roles of the microbiota and the brain, we aimed to summarize the microbiota's role with several key neurotransmitters involved in mood regulation. The focus of this paper will be on serotonin because of its strong association with neuropsychiatric disorders such as depression and anxiety. In addition, other neurotransmitters such GABA, melatonin, dopamine, norepinephrine, epinephrine, and histamine are also discussed.

The gut-brain axis

The central nervous system and the interaction with the gastrointestinal (GI) tract have historically played a significant role in multiple intestinal functions including motility, digestion, absorption, local hormone secretion, and in creating visceral sensitivity. Emerging evidence strongly suggests a bidirectional communication between the neuroendocrine system and gut microbiota and the influence they have over several aspects of brain function and behavior, including neuroendocrine responses to stress [3]. The communication between the central nervous system (CNS), intestine, and microbiota has been often referred to as the gut-brain axis, a complex bidirectional communication network between the CNS and intestines [4]. This axis involves various complex pathways such as the autonomic nervous system, enteric nervous system, endocrine system, HPA axis, immune system, and the microbiota and its metabolites [4]. Among these pathways, evidence shows that the inflammasome plays a role in the alterations associated with depression, anxiety, and other mood disorders. The existence of the link between the gut and the brain has been emphasized because of the frequent prevalence of stress-related diseases such as anxiety and depression along with gastrointestinal disorders such as IBS and IBD [5]. In the last decade, there has been evidence associating dysbiosis and disorders of the central nervous system.

Chronic stress and the associated hypothalamus-pituitary-adrenal (HPA) axis activation can negatively affect the composition of the gut microbiota through many mechanisms. Under stress, the microbial changes induced can increase gastrointestinal permeability, facilitate bacterial translocation, decrease levels of secretory IgA, modulate inflammation, and induce chronic low-grade inflammation [6]. These changes are often observed in subsets of patients with IBS and/or depression [3]. The vagus nerve connects the brain and the GI tract, and much of the communication occurs from the bottom-up, from the gut to the brain [7]. The enteric nervous system is often referred to as the “second brain”, and the interaction with the microbiota strongly influences the gut-brain axis function [8]. An imbalance of the gut microbial community can lead to inflammatory processes and activation of the HPA axis, leading to issues such as anxiety and depression. Chronic stress can also activate nod-like receptors (NLRs) family members of NLRP3, which can set off a cascade of reactions that promotes secretion of interleukin-1 (IL-1), which can induce an inflammatory response that may take part in the pathogenesis of depression [2].

Probiotics

Probiotics are microbes that provide multiple benefits, particularly alterations in the enteric nervous system and benefits in the gut-brain [7]. *Lactobacilli* and *Bifidobacteria* are the most common probiotics, as well as *Saccharomyces boulardii* and *Bacillus* species that are often found in common probiotic formulations [9]. Probiotics have beneficial effects in various clinical conditions, such as the prevention of antibiotic-associated diarrhea, constipation, sepsis, and infant allergies through various mechanisms. They can also modulate the immune system by interacting with immune cells such as dendritic cells, monocytes, and lymphocytes [9]. In addition, they can modulate intestinal function as well. For example, lactic acid bacteria (LAB) can prevent gastrointestinal dysbiosis while other strains can enhance barrier function by stimulating mucin secretion, antimicrobial activity by competing with microbial pathogens, and stimulating mucosal epithelial cells [9].

Recently, the term "psychobiotic" has been introduced to designate live bacterial strains that can influence the CNS function [10]. These microbes can influence brain cell physiology both directly and indirectly [4]. Psychobiotics and members of the human gut microbiome can produce neuroactive molecules that can modulate neural signals which can affect neurological behavior such as sleep, appetite, mood, and cognition [10]. Recent studies demonstrate microbes can produce neuroactive molecules that can directly contribute to the activity in the gut-brain axis [4]. Several studies have demonstrated that Bifidobacterium and Lactobacillus were able to improve symptoms in disorders such as anxiety, depression, autism spectrum disorder, obsessive-

compulsive disorder (OCD) [7]. The idea of treating psychiatric disorders with probiotics is not new; in 1910 Dr. George Porter Phillips demonstrated that a gelatin-whey formula containing lactic-acid-producing bacteria improved depressive symptoms in "melancholic" adults [11]. These include neurotransmitters such as acetylcholine (Ach), GABA, serotonin (SERT) that are produced by *Lactobacillus*, *Bifidobacteria*, *Enterococcus*, and *Streptococcus* species [4]. Although some promising small studies have emerged in the scientific literature, at the moment there are few clinical studies on psychobiotics.

Serotonin

Serotonin (SERT), also known as 5-Hydroxytryptamine (5-HT) is an abundant neurotransmitter that regulates emotional status and mood. It is often called the "happy hormone'' and plays a key role in appetite, emotions, motor, cognitive and autonomic functions [12]. Low metabolism of hippocampal 5-HT leads to abnormalities in brain regions associated with learning, mci memory, and emotion. It is found in the central and peripheral nervous systems, especially the enteric nervous system, and plays crucial roles in both depression and gastrointestinal function [13].

Serotonin is a monoamine transmitter derived solely from the amino acid tryptophan (Trp), one of the nine essential amino acids, and also the least abundant of all 21 dietary amino acids in human beings [14]. Tryptophan cannot be synthesized in humans and must be obtained through dietary intake or released during protein turnover [15]. Tryptophan is converted to 5-HT via the kynurenine biosynthetic pathway (KP), the main Trp catabolizing pathway. Trp metabolism is regulated in human beings by three distinct enzymes: indoleamine-2,3-dioxygenase (IDO) 1 and 2 and tryptophan 2,3-dioxygenase (TDO) [14]. TDO is the main enzyme that degrades Trp, particularly during normal physiological conditions [14]. IDO-1 becomes more important in infection [14]. The synthesis of kynurenine accounts for approximately 90% of tryptophan metabolism [16]. The 5-HT hypothesis of the pathogenesis of depression was first proposed in 1969, in which tryptophan shunts can increase kynurenine synthesis and decrease 5-HT synthesis, leading to depression [5]. The inflammation hypothesis of depression also supports the 5-HT hypothesis, as it highlights the involvement of increased expression of the rate-limiting enzyme in the tryptophan-kynurenine metabolic pathway (TDO) [17]. More recently, it has been reported that the metabolism of TRP (activated by microglia) can produce a neurotoxic metabolite known as quinolinic acid, implicated in several neurological conditions such as Huntington’s disease and depression [4]. Currently, the major therapeutic agents for treating depression are pharmaceutical antidepressants (mostly selective serotonin reuptake inhibitors or combined serotonin/noradrenaline reuptake inhibitors).

Aside from depression and mood, 5-HT is also an important neurotransmitter in the enteric nervous system and also functions to regulate intestinal secretion and motility [17]. It is produced in the intestines and the brain but also occurs throughout the body where it is considered to influence a wide variety of systemic physiological functions, including bone density and metabolism. Peripheral synthesis, which accounts for about 95% of serotonin synthesis, occurs mostly in the gastrointestinal epithelium (in the enterochromaffin cells), but also in other tissues such as bone, mammary glands, and the pancreas. 5-HT is present in the wall of the gut and acts to tie the two ends of the gut-brain axis. 90% of the serotonin required for mood, behavior, sleep, and other functions within the CNS and GI tract is produced in the gut [4]. The serotonin in the digestive system is primarily involved in regulating movement (motility) of the gut but also modulates intestinal fluid secretion and gastrointestinal sensation [18]. Therefore, disruption and downregulation of SERT can contribute to various functional gut disorders such as IBS, Crohn's disease, and ulcerative colitis [17]. For example, serum 5-HT levels are decreased in patients with IBS with constipation (IBS-C) and increased in patients with IBS with diarrhea (IBS-D). Therefore, inflammation that is associated with a dysregulation of 5-HT metabolism can be a key contributor to gastrointestinal motility dysfunction. Another mechanism involves the binding of SERT to 5-HT receptors on microglia, which induces the release of cytokine-carrying exosomes, providing a route for gut-induced neuroinflammation [4]. Although patterns are being identified, the molecular mechanisms controlling the metabolism of gut 5-HT remain unclear and more research is needed to

improve our understanding of the functions of the different pools of 5-HT in the gut [19].

Pathogenic bacteria can interfere with the synthesis and regulation of SERT. Despite the lack of clinical studies on the topic, a few studies show that disruption in the synthesis of SERT is involved in conditions such as depression and anxiety through mechanisms involving the vagus nerve [8]. Recent studies suggest that pathogens in the GI tract can disrupt 5-HT synthesis, contributing to symptoms of anxiety. For example, infections with pathogens such as *Campylobacter jejuni* (a food-borne pathogen) and *Citrobacter rodentium* have been shown to initiate anxiety-like behavior. Another pathogen, *Trichuris muris* (T. muris), has the potential to cause moderate colonic inflammation and anxiety-like behavior that was associated with immunological changes, particularly changes in the kynurenine and kynurenine/tryptophan ratios)[5]. The *Oscillibacter* and *Alistipes* type strains, a genus in the phylum of *Bacteroidetes,* have also been more abundant in depressed individuals and more abundant in patients with IBS and Chronic Fatigue Syndrome (CFS)[5]. Also, *Alistipes* species are indole-positive and may affect tryptophan availability, posing the ability to disrupt the balance in the intestinal serotonergic system)[5].

Pathogenic bacteria may be involved in infection-induced inflammation that can contribute to dysregulation in SERT metabolism. Some observe that individuals with major depression have significantly higher concentrations of a pro-inflammatory cytokine, IL-6, in comparison with controls as seen in a meta-analysis of 16 studies [20]. Antidepressants such as selective serotonin reuptake inhibitors (SSRI's) can increase the relative amounts of IL-10, a cytokine that is associated with suppressing inflammation [20]. TRP depletion is implicated in growth inhibition of certain bacteria and parasites, such as C*hlamydia psittaci, Toxoplasma gondii, and Leishmania donovani* [14]. Recent studies also report modulation of TRP metabolism in chronic viral infections, such as Human Immunodeficiency Virus (HIV), Cytomegalovirus (CMV), and Herpes Simplex Virus (HSV) [14]. IDO induction during chronic active Epstein Barr (EBV) infection is also associated with decreased serotonin levels leading to symptoms of mood disturbances. The data discussed suggests that the effects of infection and pathogens, and how they can induce changes in the microbiota, can alter metabolic pathways of serotonin production.

The presence of certain intestinal bacteria and their dysregulation could cause an over-activation of the nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) inflammasome in the brain [2]. There is significant research in recent years on the NLRP3 inflammasome and the onset of many neurological diseases such as depression, Alzheimer's disease (AD), and ischemic brain injury [2]. Over-activation of the NLRP3 inflammasome is also linked to the pathogenesis of inflammatory bowel disease, type 2 diabetes, atherosclerosis, and neurodegenerative disorders [9]. The NLRP3 inflammasome is an initiate immune signaling complex that is activated and assembled in response to pathogens or danger signals, leading to the production of pro-inflammatory cytokines such as IL-18 or IL- 1β [4]. In the CNS, the activation of the NLRP3 inflammasome in the microglia can impair the blood-brain barrier's permeability and integrity, enabling the peripheral immune cells to enter the CNS and take part in intracerebral inflammatory response through various pathways [2]. Several microbial factors can activate the intestinal inflammasome, which may lead to the production of effector molecules that influence the CNS via the vagus nerve. Targeting NLRP3 inflammasome therefore can become a new target for improving depression treatment outcomes in the future [2].

Abnormal SERT expression can also contribute to a variety of functional GI disorders such as chronic constipation [19]. This is often accompanied by a decreased abundance of *Clostridium, Lactobacillus, Desulfovibrio,* and *Methylobacterium* and an increased abundance *of Bacteroides* and *Akkermansia,* leading to damage of the intestinal barrier. The prolonged residence time of feces in chronic constipation patients may lead to additional intestinal dysbiosis, which may further affect the intestinal immune function, motility, and barrier function [21]. Therefore, the current data suggest that gut dysbiosis could upregulate the expression of intestinal SERT in the intestine, and then increase the uptake and resolution of intestinal 5-HT to inhibit intestinal motility, causing constipation [21]. Future studies are required to determine whether particular members of the

microbiota alter host 5-HT biosynthesis to support colonization, growth, or resilience of particular gut microbes. The additional data can further delineate dietary and/or supplementation strategies that may therapeutically modulate disorders that are affected by shifts in the microbiome.

Probiotics and Serotonin

Probiotic administration can influence the availability of tryptophan, the serotonin precursor. For example, *B. infantis* can affect metabolites of 5-HT with subsequent anti-inflammatory effects and normalization of depression-like behavior. The decrease of pro-inflammatory immune responses (such as IFN-γ, TNF-α, and IL-6), and the elevation of tryptophan by *Bifidobacteria* treatment supported the suggestion that *B. infantis* may possess antidepressant properties [5]. The probiotic *Bifidobacterium infantis 35624* resulted in the reversal of depression-like behavior deficits, *Lactobacillus helveticus NS8, Bifidobacterium longum*, and *Lactobacillus rhamnosus* increase the levels of the 5-HT in the hippocampus of rodents [1].

A study by Cao et al. revealed that *L. acidophilus* and *B. longum* could increase the expression of serotonin in intestinal epithelial cells [21]. According to Wang et al., *L. rhamnosus* is one of the best-studied *Lactobacillus* strains in clinical trials and can increase the expression of serotonin, inducing remission and preventing recurrence of IBD. *B longum, B. infantis, and L. rhamnosus* showed higher 5-HT content in the frontal cortex, and higher expression of 5-hydroxytryptophan (5-HTP). In a study with mild-stress induced mice treated with *B. longum* and *L. rhamnosus*, higher tryptophan hydroxylase (TPH) but lower IDO was observed in the prefrontal cortex and hippocampus [1]. A recent study by Yaghoubfar et al., [22] discussed an association with *Akkermansia muciniphila* and its extracellular vesicles (EVs) on gene expression of the serotonergic system in the colon and hippocampus, promoting both serotonin concentration and signaling/metabolism through the gut-brain axis, though the exact mechanism are not clear [22]. The results of these studies suggest that using probiotics to modulate microbiota could be used therapeutically to modulate neurotransmitters to treat disorders associated with neurotransmitter imbalance. Collectively, these studies suggest that microbiota manipulation using probiotics could be a valid therapeutic strategy in neurotransmitter expression and the conditions that relate to them” [23].

Recent data show that probiotic intake is also related to the NLRP3 inflammasome attenuation and lower levels of pro-inflammatory markers [9]. In the review paper by Kasti et al. (2021), there were reports of reduction in NLRP3 induced inflammation with various strains such as *Lactobacillus johnsonii, Lactobacillus rhamnosus, Bacillus fragilis, Bacillus subtilis,* and *Enterococcus faecalis* [9]. Considering the role of the NLRP3 inflammasome and depression, targeted probiotics that can modulate the NLRP3 inflammasome could be offered as an affordable strategy to treat neurological disorders such as depression.

GABA

Gamma amino butyric acid (GABA) is the main inhibitory neurotransmitter, playing a key role in anxiety and depression in mammals [10]. GABA is involved in regulating blood pressure and heart rate and plays an important role in the perception of pain and anxiety [10]. GABA is synthesized by a pyridoxal-5'-phosphate (PLP) dependent glutamate decarboxylase (GAD) enzyme by the irreversible a-decarboxylation L-glutamate (GLU) [10]. GLU is one of the most abundant amino acids in nature and can act as an excitatory neurotransmitter because of the interaction with specific receptors [24]. Many gram-positive and gram-negative bacterial strains can convert the main stimulatory neurotransmitter glutamate (Glu) to GABA. Among the Gram-negative bacteria able to produce GABA are *the Escherichia coli* (E. Coli) bacterial strains [25], and *Pseudomonas* [26]. Metagenomic data from the Human Microbiome Project show that genes encoding for GAD could be present in a significant portion of the human gut microbiome [27]. According to Pokusaeva and colleagues, the genomes of 26 unique genera were found to possess glutamate decarboxylase orthologs. These include intestinal bacteria such as *Bacteroides spp*. (RA, 31.7%), *Escherichia spp*. (RA, 22.5%), and *Fusobacterium spp*. (RA, 9.9%)[28].

GABA levels and GABA receptor activity play a role in anxiety disorders, though the exact mechanism is not fully understood [29]. Clinical research, using pharmaceutical drugs targeting GABA receptors, suggests an overall lower level of GABA neurotransmission in anxiety disorders [30]. It is suggested that the changes in the expression of GABAergic receptors are involved in the pathogenesis of anxiety and depression. In addition to anxiety, low levels of GABA in the central nervous system are associated with depression and insomnia [31]). Several studies have demonstrated the beneficial effects of GABA on sleep. For example, Mabunga, Gonzales, Kim and Choung [32] found that GABA extracts from fermented rice could counter sleep disturbance induced by caffeine in mice. In another prospective trial on 114 adult patients diagnosed with insomnia, GABA derived from rice germ was shown to improve sleep latency [33].

Probiotics and GABA

Of clinical interest in the treatment of conditions reflective of low GABA levels is the potential use of probiotics to deliver GABA or to modulate GABA receptor activity. According to Sarkar and colleagues, probiotics may differentially alter the expression of inhibitory GABA receptors in a region-dependent manner, modulating regional excitation-inhibition balance. As a result, these changes may be linked to reductions in anxiety-and depression-related behavior [34]. The GABA-producing LAB strains belong to the *Lactobacillus, Lactococcus, Streptococcus,* and *Bifidobacterium* genera, Li and Cao [35]. According to Li and Cao, GABA production is more a function of strain than genera. Of particular interest are the health-promoting lactic acid bacteria strains, such as *L. brevis* that are among the best GABA producers.

In a study by Duranti et al., 2020 [10], they identified seven different bifidobacterial species that express GAD genes in their genomes. These include *B. adolescentis, B. angulatum, B. dentium, B. merycicum, B.moukalabense, B. ruminantium and B. samirii* [10]. It is noteworthy that *B. adolescentis* strains the highest level of prevalence of GAD genes in their genomes, suggesting this strain as a model GABA producer within the *Bifidobacterium* genus, showing an intriguing association between *B. adolescentis* and mental disorders such as anxiety and depression [10].

Another probiotic strain that has gained much attention regarding GABA regulation is *L. rhamnosus*. One landmark study explored the behavioral and physiological effects of administration of *L. rhamnosus* (JB-1) in mice [36]. *L. rhamnosus* dramatically altered GABA activity in the brains of the mice and affected how well they responded to stress. Changes in the expression of GABA receptors were detected in several areas of the brain, including the amygdala and hippocampus (Strandwitz, 2012). In a study by Vlainic and colleagues, it has been shown that intestinal bacteria can produce GABA involved in the regulation of many physiological and psychological processes. Treatment with *L. rhamnosus* has been shown to induce region-dependent alterations in the expression of GABA receptors in the brain [5]. Another study by Jenkins and colleagues showed that chronic treatment with the lactic acid bacteria, *L. rhamnosus* in mice induced alterations in GABA receptors in cortical hippocampus and amygdala, while also reducing stress-induced corticosterone levels and anxiety- and depression-related behavior [16]. The ability of *L. rhamnosus* to alter behavior via the GABAergic response via the vagus nerve supports the theory that GABA-modulating bacteria can affect host behavior [37].

Another bacterium capable of secreting GABA is *Bifidobacterium dentium*, which might play an inhibitory role in inflammation and modulating visceral sensitivity in the intestine [27]. *B. dentium* can survive the harsh acidic environment of the intestine and may have abundant amounts of genes encoding for GAD, making it another model organism for GABA-producing microbes [27]. Although several probiotic supplements containing GABA-producing strains are already being marketed for their effects on mood, more research into the effects of specific strains is warranted.

Melatonin

Melatonin is a natural neurotransmitter-like compound produced primarily by the pineal gland but

can also be produced in the gastrointestinal tract [38]. In mammals, biosynthesis of melatonin starts with the conversion of the amino acid tryptophan (TRP) to 5-HT to serotonin via a PLP dependent enzyme 5-hydroxytryptophan decarboxylase. Melatonin synthesis is promoted by norepinephrine and requires serotonin as a precursor [39]. The daily pattern of melatonin secretion carries information for circadian and seasonal temporal organization [39]. Other organs that use activated immune-component cells to synthesize melatonin include the skin, GI-tract and lungs [39]. These immune-component cells include monocyte-derived and resident macrophages, microglia, and lymphocytes [39].

Melatonin is involved in regulating many biological and physiological body functions, such as transducing light-dark information to the whole body [39]. According to Malhotra et al. [38] melatonin has a diverse role in the human body. These include regulating the circadian rhythm disturbances and sleep disorders; facilitating “sundowning” in patients with Alzheimer’s disease; modulating immunity, stress response, and certain aspects of aging; and playing a role in antioxidant defenses to remediate oxidative stress [38]. Melatonin is involved in various aspects of the innate immune response, such as the reduction of nocturnal melatonin to promote the mobilization of leukocytes [39]. The synthesis of melatonin by macrophages/microglia can increase its phagocytic ability to reduce oxidative stress to take part in the recovery phase of the inflammatory response [39].

There is emerging evidence that melatonin can play a role in neurological conditions such as depression. Since the monoaminergic systems that underlie major depressive disorder (MDD) and melatonin production overlap, melatonin is involved in neuroplasticity [39]. Mood alterations have been studied in models of circadian disruptions. For example, varied depressive symptoms have been observed in seasonal affective disorder, diurnal variations in mood have been observed in naturalistic conditions, and experimental studies have demonstrated an interaction between circadian phase and duration of prior wakefulness affects mood [39]. In animal models, melatonin treatment can significantly reduce the effects of lipopolysaccharide (LPS) and reduced NF-Kb in the cortex and hippocampus, resulting in improvements in depressive symptoms and behaviors [39].

According to Eliasson [40], melatonin also plays a significant role in modulating gut-related conditions. These include reducing abdominal pain in people with inflammatory bowel syndrome (IBS), improving ulcer healing, and preventing harmful substances from damaging the intestinal epithelium [40]. There has been considerable research into the association of IBS and depression with the gut-brain axis and alteration in gut microbes over the last few years [41]. Cytokines and inflammatory markers such as interleukin (IL)-6 and IL-10 are among the many mediators of inflammation and are at the forefront of intestinal inflammatory conditions such as IBS [41]. According to Mudyanadzo et al., the inflammation alters gut microbes and permeability of the gut mucosa, leading to enhanced translocation of neurotransmitters and subsequent activation of the hypothalamic-pituitary-adrenal (HPA) axis which is intrinsic to the pathophysiology of depression [41].

Considering the role of dysbiosis on NLRP3 inflammasome activation, the subsequent pro-inflammatory cytokine responses and the reports of neuroinflammatory responses in neurodegenerative and psychiatric disorders, melatonin’s role in intestinal inflammatory conditions may provide an indirect approach to treatment opportunities for psychiatric disorders such as depression.

Probiotics and Melatonin

Lactic acid bacteria (LAB) including *L. bulgaricus, L. acidophilus, L. casei, L. plantarum* can synthesize melatonin [42]. Wong et al. [43] studied the effects of a probiotic (VSL#3) on symptoms, psychological and sleep parameters, and pain sensitivity in people with irritable bowel syndrome. VSL#3 is a probiotic compound that contains multiple strains of three viable lyophilized bacteria species: three strains of *Bifidobacterium* (*B. longum*, *B. infantis* and *B. breve*); four strains of

Lactobacillus (*L. acidophilus*, *L. casei*, *L. bulgaricus* and *L. plantarum*); and one strain of *Streptococcus* (*S. salivarius* subspecies *thermophilus*). The results showed that the participants, who took the probiotics, saw a significant decrease in abdominal pain duration and distension intensity and an increase in rectal distension pain thresholds. The results also showed an increase in salivary morning melatonin levels in the male participants who were treated with VSL#3, and this was associated with improved satisfaction in bowel habits. These results propose probiotics may act by influencing melatonin production which leads to a reduction in irritable bowel syndrome symptoms [43], which may subsequently improve mood disorders as a secondary benefit [41].

In a study by Jiao et al. [44], researchers looked to isolate and identify root-dwelling, endophytic bacteria from three grapevine varieties. What researchers found was that when the bacteria were cultured in a laboratory, some bacteria strains exuded melatonin. In particular, *Bacillus amyloliquefaciens* SB-9 showed the highest level of *in vitro* melatonin secretion and also produced three intermediates of the melatonin biosynthesis pathway. In addition, other bacteria strains secreted melatonin including, in part, *B. thuringiensis* CS-9 and *Agrobacterium tumefaciens* [44]. The findings of this study demonstrate that some endophytic bacteria have melatonin producing ability that promote endogenous melatonin production in plants, although the mechanisms remain unclear [44]. More investigations are needed to identify the role of melatonin biosynthesis in naturally occurring symbiotic relationships between certain microbes and their host to evaluate their influence on neurotransmitters and their effect on mood disorders.

Catecholamines

Catecholamines (CATs), also known as the "stress hormones", are a set of monoamines comprising a catechol group and an amine side chain. They are known to interact with both the endocrine system as well the nervous system, which is why they are often interchangeably called hormones and neurotransmitters. Three common ones are norepinephrine (noradrenaline), epinephrine (adrenaline), and dopamine [45]. Chromaffin cells of the adrenal medulla and adrenergic and dopaminergic neurons produce all three catecholamines [46]. CATs are derived from L-tyrosine, obtained from either dietary sources or synthesized from phenylalanine in the liver and other tissues. Dopamine, found in the central nervous system, is the first catecholamine synthesized, which is then enzymatically converted to noradrenaline and adrenaline [47].

The communication between microbes and CATs can be considered bi-directional. Dysbiosis of gut microbes, for example, can interfere with the synthesis and regulation of CATs from a bottom-up direction. Certain strains such as *Escherichia, Bacillus*, and *Saccharomyces* produce norepinephrine. *Bacillus* and *Serratia* can produce dopamine [48]. CAT's can also modulate the activity of microbes from a top-down direction. Epinephrine is found to be one neurotransmitter that can modulate the motility of a specific microbe *P. fluorescens* MFN1032by increasing the swarming motility [49]. Norepinephrine can increase the growth of *S. typhimurium* within Peyer's patches, as seen in mouse models. Similarly, incubation in vitro with norepinephrine enhanced the growth of this and other gastrointestinal and oral bacteria including *Fusobacterium nucleatum, Tannerella forsythia, E. coli, Enterobacter spp., Shigella sonnei,* and *C. jejuni*" > [50].

The CATs including dopamine, dopamine-4-O-sulfate, epinephrine, norepinephrine, and norepinephrine-3-O-sulfate have been associated with neurochemical production within the gut microbiome and it has been found that their neurochemicals can influence host physiology and/or behavior [51]. Stress-related hormones, such as noradrenaline, can control bacterial gene expression and the signals that are sent between bacteria. The effects of stress mediators, such as norepinephrine, on the intestinal epithelium, can increase cecal-colonic adherence of *E. coli* strains and has been shown to change *Salmonella* and *E. coli* uptake into Peyer's patches [51]. However, Collins et al. [52] noted that besides stress, gut bacteria and neurotransmitters may also be influenced by many other circumstances, such as changes to the diet, travel, antibiotic use, or other pharmaceuticals that can slow the gut transit time. In summary, complex bi-directional communication occurs between microorganisms and their host via chemical signals such as the

ones discussed. A greater understanding of the mechanisms involved in this bi-directional communication could lead to strategies for therapeutic applications.

Catecholamines, along with other neurotransmitters mentioned earlier, are showing a pretty significant role in gastrointestinal (GI) physiology. CATs have multiple roles in the GI tract, including but not limited to, regulating gut motility, aiding in nutrient absorption, gastrointestinal immunity, and in the microbiome [45]. What has gained the most attention recently is CATs ability to influence microbes in bacteria inhabiting the GI tract, particularly *E. coli, Salmonella, H. pylori, Listeria, Campylobacter and Yersinia* [47]. Some studies have shown that catecholamine stress hormones can influence growth, motility, biofilm, information, and/or virulence of intestinal pathogens such *Escherichia coli* and *Salmonella* spp. [53]. They demonstrated this in 1992 when Lyte and Ernst showed in experiments that noradrenaline and adrenaline could significantly increase the growth of *E. coli*, *Yersinia enterocolitica*, and *Pseudomonas aerugiosa* [47]. In 1999, further research indicated that CATs were widespread among both Gram-negative and Gram-positive bacteria [47]. However, the increase in growth depended on the type and concentration of the CAT to which the bacteria were exposed [46].

To date, most microbial endocrinology investigations have focused on bacteria's interaction with stress-associated, "fight or flight" biochemicals such as CATs, because of a historic observation that mammals showed an increased risk of developing an infection after periods of exposure to stress [47]. Their role is essential in their ability to cross-talk between the microbes and the immune system [50]. CATs have also revealed the potential impact of these compounds on bacterial infections in humans [46]. CATs, including noradrenaline, are also known to alter gene expression in some bacteria and this results in the preferential growth of some communities [52].

Interestingly, CATs may be associated with an increase of complications related to stress, such as periodontal disease or disorders of the skin such as staphylococcus (Freestone, 2013). For example, noradrenaline, adrenaline, and dopamine were all able to increase staphylococcal growth [47]. Intestinal overgrowth of *E. coli* has also been implicated in laboratory mice when exposed to psychological stress such as restraint . Physically stressing mice by surgery or a short-term period of starvation was found to increase the numbers of *E. coli* adhering to the cecal mucosa when compared to the control [47]. Another study showed elevated plasma noradrenaline and adrenaline levels increased the susceptibility of stressed mice to *Chlamydia trachomatis* infection [47]. Psychologically stressed mice exhibited altered microbial diversity that increased their susceptibility to *C. rodentium* in a way that established an infection [47]. Studies demonstrate CATs can influence pathogen susceptibility to a host defense response. This has been seen with the ability of *Salmonella* to downregulate a host's resistance to antimicrobial peptides while influencing oxidative stress homeostasis in cells [54]. The results of these studies suggest that the microflora can sense psychological and physical stress [47]. In addition, stress can increase the virulent activity of the microflora (including pathogenic microbes)[47].

Probiotics and CAT’s

There is promising research indicating the role of probiotics and modulation of CATs. A balanced production of the CATs is critical in the management of pathogenic invasion. However, it should be noted that there are still limited studies because of the lack of actual data about luminal catecholamines. Probiotic treatment, such as with *Bifidobacterium*, has demonstrated the ability to modulate behavior, normalize the immune response, and restore basal norepinephrine (NE) concentrations in the brain stem ("Psychobiotics: A Novel Class of Psychotropic - Biological Psychiatry," n.d.). It is becoming apparent that various bacterial strains are associated with CATs such as NE and dopamine. *Lactobacillus rhamnosus* and *Lactobacillus helveticus* were shown to prevent stress-induced memory dysfunction and normalize brain-derived neurotrophic factor (BDNF) expression in the CA1 region of the hippocampus [52]. *L. plantarum* can cause positive changes in emotional behaviors through increasing dopamine and SERT, lowering stress hormones, and reducing inflammation [55]. *Escherichia* and *Streptoccocus* probiotic strains can produce

norepinephrine [56], while B*acillus* and *Serratia* produce dopamine [57]. Interestingly, various probiotics such as *L. acidophilus, B. infantis, B. longum*, and intestinal microbes such as *Candida* and *Streptococcus* have been found to produce psychotropic effects either by secreting neurotransmitter molecules (such as CATs) or by regulating endocannabinoid receptor expression [58].

Histamine

Histamine is one of several, excitatory (stimulating) neurotransmitters. Histamine is synthesized from histidine via the histidine-decarboxylase enzyme (HDC) [59]. Histamine is traditionally known for the role it plays in allergic reactions [60]. However, histamine is also involved in neurotransmission and can have a major impact on people's emotions and behavior [61]. A growing body of evidence suggests that histamine acts directly on neurons and neuronal structures, and is an active neuromodulator in the developing brain, playing an important role in brain development [62]. Experimental studies show that there are functional interactions between the serotonergic and histaminergic systems that share functions that are often impaired in depression such as appetite, cognition, emotion, and sleep [59]. Histamine H1-receptor activation increases the firing rate of serotonergic neurons, and reduced H1-receptor density is observed in depressed patients that correlate with severity of symptoms [59]. Histamine is also involved in regulating the sleep-wake cycle, and in promoting the release of other excitatory (stimulating) neurotransmitters, epinephrine, and norepinephrine [63].

Recent research has identified that systemic inflammation may render some antidepressants ineffective in some people, and histamine may be to blame. According to Munari et al. [59], failure to respond to selective serotonin reuptake inhibitors (SSRIs) may result from abnormalities of neurotransmitter systems that excite serotonergic neurons such as histamine [59]. Research from Dr. Parastoo Hashemi (Imperial College of London, 2021) shows that histamine is a potential key player in depression. Their experiments showed that brain serotonin levels dropped within minutes of LPS injection; it is hypothesized that histamine may have triggered inflammation in the brain, directly inhibiting the release of serotonin by attaching to inhibitory receptors on serotonin neurons (Imperial College of London, 2021). These findings can open new avenues to explore histamine as a causative agent of depression while allowing the development of novel strategies that reduce histamine in the brain to treat depression (Imperial College of London, 2021).

Histamine moves throughout the bloodstream and can affect the gut, lungs, skin, brain, and the entire cardiovascular system. Once histamine is formed it is stored or broken down by an enzyme in either the central nervous system or digestive tract. According to Leech (2018) histamine is produced in the body and is also contained in certain foods. About 1% of the population suffers from adverse reactions to foods that have a normal histamine level (Leech, 2018). These adverse reactions or sensitivities to histamine are known as histamine intolerance (Leech, 2018). The primary enzyme that degrades ingested histamine is diamine oxidase (DAO) through the consumption of foods rich in histamine [64]. A deficiency of DAO is associated with an increased risk factor that a person will develop histamine intolerance[64]. According to Leech (2018) and Raje et al. [65], there are many reasons a person may have lowered levels of DAO. These include the overuse of antibiotics, irritable bowel syndrome (IBD), consuming foods high in histamine, small intestinal bacterial overgrowth (SIBO), and single nucleotide polymorphisms (SNPs) can affect the level of activity of DAO.

Probiotics and Histamine

It has been demonstrated that certain strains of bacteria can either produce histamine or degrade histamine. Histamine intolerance may be improved by avoiding the probiotic strains that produce histamine and ensuring the consumption of strains that degrade histamine. Histamine-producing bacteria strains include *L. reuteri*, *L. casei*, and *L. bulgaricus* [66,67]. Histamine-degrading strains include *L. rhamnosus*, *L. plantarum*, and Bifidobacteria [68-70]. According to Thomas et al. [66]

beneficial microbes such as *Lactobacillus reuteri (L. reuteri)* can play a role in producing biologically active compounds that can regulate the mucosal immune system. Some fermentative bacteria including some strains of *Lactobacilli* spp. can produce histamine from L-histidine through the histidine decarboxylase enzyme. The study concluded that *L. reuteri,* which is a component of the gut microbiome, can transform L-histidine (dietary component) into the immunoregulatory signal, histamine, which suppresses proinflammatory TNF production [66].

Nealon et al. (2017) also found a positive relationship between histamine and *Lactobacillus reuteri (L. reuteri).*The study focused on the human rotavirus (HRV), which is the leading cause of severe childhood diarrhea. Histamine was also positively impacted in this study. In this study, histamine decreased 0.19-fold in the LIC metabolites and increased 1.57-fold in the serum of probiotics and rice bran group as compared to the probiotic group only. Previous investigations with *Lactobacillus reuteri* also showed that probiotics can use a bacterial-derived histidine deacetylase to convert dietary histidine into histamine in the colonic lumen, which can act on H2 receptors to suppress colonic inflammation and reduce damage to the colonic epithelium (Nealon et al., 2017). A study by Gao et al. [71] showed that defined probiotic strains of *Lactobacillus reuteri (L. reuteri)* suppress intestinal inflammation. *L. reuteri* is a beneficial microbe that has been used as a probiotic for over two decades. Reports show that *L. reuteri* works to suppress proinflammatory cytokines in the intestinal epithelial cells and monocytes and can play a role in reducing intestinal inflammation [71] . These are important findings because incorporating these specific beneficial probiotic strains as part of a person's care plan can suppress intestinal inflammation in disorders such as IBD [71]. Because of the growing evidence showing increased inflammation in depressed individuals (as evidenced in elevations in inflammatory biomarkers), and the association with intestinal disorders such as IBD and inflammation [72], strategies to reduce intestinal inflammation may prove beneficially therapeutically in the treatment of neurological conditions such as depression.

Conclusion

The latest research demonstrates that the human microbiome plays a vital role in regulating human health, particularly mental health. It is well established that the microbiota are a significant player, both negatively and positively, in regulating critical neurotransmitters that affect the human body. Research shows that pathogenic, commensal, and probiotic bacteria play a critical role in influencing the functioning of many important neurotransmitters. Research also shows that these neurotransmitters take part in regulating important functions of the body, such as gastrointestinal motility and secretions, hormonal balance, and the neuroimmune axis, which affects depression and mood states. Psychobiotics research offers viable solutions for individuals who are suffering from conditions associated with dysregulation of neurotransmitters because of compromised gut microbiota. These solutions may offer viable alternatives to current options that can be invasive and often have some undesirable side effects.

However, this field is still in its infancy, and there is a vast amount of opportunity for future research on this topic. Further studies should evaluate mechanisms of microbial action and the further development of probiotics and functional foods that may aid in the therapy of chronic ailments associated with disruptions of the microbiome. These conditions include but are not limited to, depression, anxiety, autism, multiple sclerosis, as well as various gastrointestinal and metabolic disorders. The growing prevalence of these conditions, despite the availability of pharmaceuticals, demonstrates that viable alternatives are in need. The future looks promising, as scientists continue to unravel the mechanisms that underlie the gut-brain axis, to facilitate methods to manipulate gut microbiota. These findings might lead to innovative therapies for the management of disorders of the neuroendocrine system.

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