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Gut-Brain Nexus: Deciphering the Role of Gut-Derived Neurotransmitters Serotonin and GABA in Neurological and Mental Health

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KEYWORDS

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ABSTRACT:
Background

This article is a review aiming to investigate into the intricate relationship between the gut and the brain, with a specific focus on two pivotal gut-derived neurotransmitters, Serotonin and Gamma-Aminobutyric acid (GABA). Emerging research suggests that the gut microbiome, through the production of these neurotransmitters, plays a critical role in influencing neurological and mental health. Growing data indicates that the gut microbiota regulates the appropriate operation of the gut-brain axis. Approximately 90-95% of the body's serotonin, a key modulator of mood and emotion, and a substantial portion of GABA, a primary inhibitory neurotransmitter involved in reducing neuronal excitability, are synthesized in the gut.

Main text

This review explores the mechanisms by which these gut-derived molecules communicate with the brain, involve in the physiology of the gut-brain axis via complex neural, endocrine and immune pathways. The implications of this bidirectional communication for a spectrum of neurological and psychiatric disorders are considered. By integrating findings from recent studies, a comprehensive understanding of how alterations in gut microbiome composition and function can influence brain health and behavior are analyzed in this article. Furthermore, the review discusses therapeutic potentials, highlighting how modulation of the gut microbiome could offer novel approaches to treating mental health disorders in relation with Serotonin and GABA.

Conclusions

This summary of recent findings highlights the importance of the gut-brain axis as a key focus for psychoneurological health and lead ways for novel, microbiome-focused approaches in psychiatry and neurology.

INTRODUCTION

The gut-brain axis refers to the bidirectional communication between the gastrointestinal tract and the brain. This communication involves neural, hormonal and immunological signals. It involves a complex network of communication between the central nervous system (CNS) (brain and spinal cord) and the enteric nervous system (ENS) (nerves within the gastrointestinal tract). This communication occurs through various channels, including the bloodstream or the vagus nerve

(VN), which connects the brain to the gut, allowing them to influence each other. On the neural level, signals travel between the gut and the brain, influencing processes such as digestion, nutrient absorption and feeling of satiety. Hormones released by the gut can also affect brain function and vice versa and this axis plays a crucial role in various aspects of health, including digestion, mood regulation, and immune function. Imbalances in this communication may contribute to conditions such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD) (Frank et al., 2007), and certain mental health disorders like depression, anxiety, schizophrenia, Alzheimer’s and Parkinson.

The ENS, often referred to as the "second brain," is a complex network of neurons lining the gastrointestinal tract. It is crucial in determining mood and overall wellbeing since it has the ability to regulate gut behaviour separately from the brain in the head. It is involved in several body processes, including digestion, and has about 100 million neurons. Research on the ENS is developing and provides fresh perspectives on how it affects the body and mind .

The gut microbiome influences the production of neurotransmitters in the gut, which then interact with the brain via the gut-brain axis, a complex communication network. This interaction plays a crucial role in regulating mood and emotional well-being, with imbalances potentially linked to mental health issues like anxiety and depression. Thus, the gut microbiome and its neurotransmitter production are integral to understanding and potentially treating various mental health conditions. Research in this field is growing and revealing the impact of the gut-brain axis on various aspects of health. Lifestyle factors such as diet, stress management, and probiotic use can potentially influence this axis and contribute to overall well-being.

The Gut Microbiome

The human gut is home to trillions of bacteria, a vast community of microorganisms collectively known as the ‘gut microbiota’ or the ‘gut microbiome’. These microbes play a crucial role in the gut-brain axis by producing bioactive compounds that can influence neural function and immune responses (Y. Chen et al., 2021). They help break down certain foods, especially complex carbohydrates, fibers, and some proteins and fats, aiding in digestion and nutrient absorption. They play a critical role in developing and maintaining the immune system, training immune cells, and protecting against harmful pathogens. These microbes synthesize essential vitamins like vitamin K and B, other beneficial compounds. They also help in the production of neurotransmitters, interaction with the nervous system, and modulation of inflammation, the gut microbiome can influence mental health and mood . The balance and composition of the gut microbiome are crucial for overall health (Clapp et al., 2017; H.-J. Wu & Wu, 2012, 2012). Factors like diet, lifestyle, medications, and genetics can all impact this delicate ecosystem. Research continues to uncover the vast and intricate ways in which the gut microbiome contributes to health and disease.

These microbes are not just passive residents, but they actively interact with our body in many ways. One of the key ways the gut microbiome interacts with the brain is through chemical messaging. They can produce various substances, including neurotransmitters like serotonin and GABA, which play roles in mood regulation. These chemicals can travel from the gut to the brain, either through the bloodstream or via the VN, a direct neural pathway connecting the gut and the brain. They can influence our mood, emotions, and even behavior. For instance, a healthy gut microbiome that produces a balanced amount of serotonin may contribute to a feeling of well-being and happiness. Conversely, an imbalance in the gut microbiome (called dysbiosis) might lead to reduced production of these beneficial substances, potentially contributing to mood disorders like depression or anxiety (Clapp et al., 2017). They also play a role in regulating inflammation in the body. Chronic inflammation, which can be influenced by an imbalanced microbiome, is thought to be a risk factor for several mental health conditions, including depression (Baj et al., 2019; Y. Chen et al., 2021). The gut-brain axis is also involved in how our body responds to stress. Stress can affect the composition of the gut microbiome, and in turn, these changes in the gut can influence our stress response and emotional state (Geng et al., 2020). There is a two-way communication between the gut and the brain. Not only does the gut microbiome affect the brain, but the brain can also influence the composition and function of the gut microbiome. This interaction creates a feedback loop where the gut and brain continually influence each other bringing about significant implications for our mental health (Clapp et al., 2017). This highlights the importance of maintaining a healthy gut microbiome as part of overall mental and emotional well-being.

The percentage of different types of bacteria in the gut varies greatly among individuals, influenced by factors like diet, genetics, environment, and overall health. It's important to note that these percentages are approximate and can vary widely. The gut microbiome is highly dynamic and can change in response to diet, lifestyle, medication, age, and health status. Maintaining a diverse and balanced gut microbiome is considered important for good health, particularly for its role in digestion, immune function, and even mental well-being (H.-J. Wu & Wu, 2012).

Neurotransmitters are chemical messengers that are essential for gut-brain communication, and the generation and control of these messengers are greatly influenced by the gut microbiome. In particular, the gut microbiota can produce neurotransmitter precursors, stimulate the local nervous system, and impact brain function and cognition by producing a variety of neuroactive metabolites, including neurotransmitters and their precursors. It can also catalyse the synthesis of neurotransmitters through dietary metabolism (Y. Chen et al., 2021; Dicks, 2022; Miri et al., 2023). For instance, GABA, dopamine, norepinephrine, serotonin, and histamine are the main neurotransmitters that gut bacteria employ to connect with the CNS (Dicks, 2022). Neurotransmitters and gut microbiota have also been linked to emotional distress. For example, serotonin levels were positively correlated with Proteobacteria abundance, and norepinephrine was positively correlated with Bacteroidetes but negatively correlated with the Firmicutes phylum. This reciprocal relationship between the gut microbiota and neurotransmitters emphasises the gut microbiota's function in emotional discomfort and neurotransmitter modulation (Barandouzi et al., 2022). Understanding the relationship between the gut microbiome, its neurometabolic interactions, and its association with brain health and diseases is the focus of the fascinating new field of neuromicrobiology (Miri et al., 2023). Thus, the control of neurotransmitters, which in turn impacts many facets of brain function and cognition, is greatly influenced by the gut microbiome.

The Role of Gut-Neurotransmitters

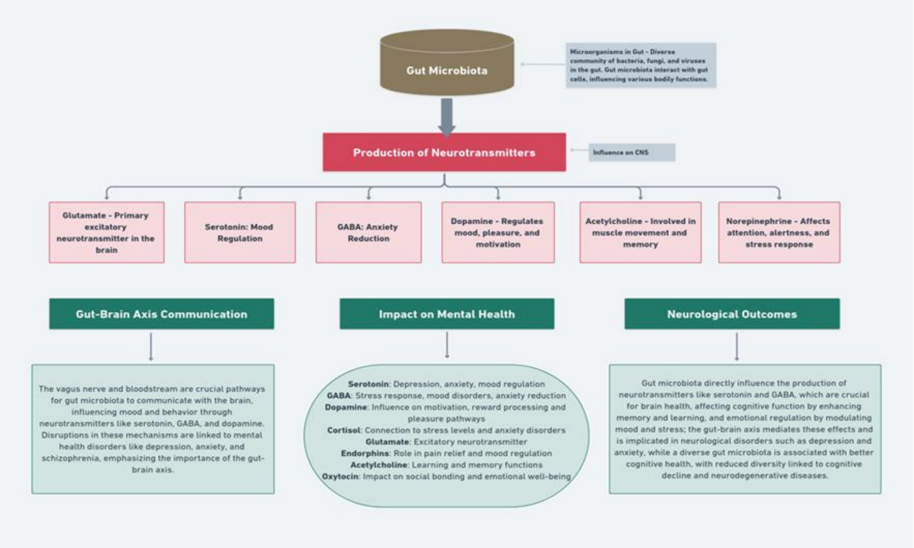
The influence of gut-derived neurotransmitters on mood and cognitive functions is a complex and interrelated that intertwines neurology, gastroenterology, and psychology. The importance of these neurotransmitters lies in their influence on the gut-brain axis. They can affect the physiological processes in various ways. Mood and emotional well-being are regulated by these neurotransmitters. For instance, Serotonin, often referred to as the ‘feel-good’ neurotransmitter, have been linked to mood disorders such as depression and anxiety. The gut's production of serotonin contributes to emotional stability. Neurotransmitters in the gut influence the regulation of digestive functions, including peristalsis and the secretion of digestive enzymes, efficient nutrient absorption and overall digestive health. Neurotransmitters like serotonin and ghrelin are involved in the regulation of appetite and satiety. Communication through neurotransmitters in the gut also plays a role in regulating the immune system. This helps in maintaining a balance between immune responses and preventing excessive inflammation (Dinan & Cryan, 2017). Similarly, other bacteria in the gut can produce GABA, which is known for its calming effect on the brain and regulates the feelings of anxiety and stress.

The exact number of neurotransmitters produced in the gut is not definitively known. However, the gut is known to produce a variety of neurotransmitters, with some of the most significant ones being Serotonin, GABA, Dopamine, Norepinephrine, Acetylcholine and Glutamate. About 90-95% of the body's serotonin, a key neurotransmitter involved in regulating mood, appetite, and sleep, is produced in the gut (Appleton, 2018; Barandouzi et al., 2022). GABA is an inhibitory neurotransmitter, which helps control fear and anxiety when neurons become overexcited, is also produced by certain gut bacteria (Liu et al., 2022; Otaru et al., 2021). A small but significant amount of dopamine, which plays roles in how we feel pleasure, is also produced in the gut (Y. Chen et al., 2021; Sittipo et al., 2022; Xue et al., 2018). Some amount of Norepinephrine is produced in the gut, and it is an important neurotransmitter for attentiveness, emotions, sleeping, dreaming, and learning (Asano et al., 2012; Zhou et al., 2005). Acetylcholine is also produced in the gut and is involved in learning and memory, and it is also essential for bowel movement (Y. Chen et al., 2021). Glutamate is a key excitatory neurotransmitter important for learning and memory, with some production occurring in the gut (Tomé, 2018). This is not a complete list, and more study is being done to understand the gut's function in the

synthesis of neurotransmitters and how it affects health and illness in general. The gut microbiome plays a crucial role in this process, as many of these neurotransmitters are produced by or influenced by the gut bacteria.

There are several key neurotransmitters like Norepinephrine (Noradrenaline), Epinephrine (Adrenaline), Histamine, Substance P, Vasoactive Intestinal Peptide and Somatostatin, that are not predominantly produced in the gut, but play significant roles in the physiological processes of the gut. These neurotransmitters are mainly produced in the brain or other parts of the nervous system but have important effects on gut function and are essential to many gut processes, indicating the complex interactions between different systems in the body. In order to understand different gastrointestinal problems and their relationship to general health and disease, it is important to gain insight into the interplay between these neurotransmitters and the gut. Norepinephrine (Noradrenaline) is primarily produced in the brain and adrenal glands. It influences gut motility, blood flow, and the intestinal lining's integrity. It plays a role in the stress response, which can significantly affect gut function (Asano et al., 2012; Barandouzi et al., 2022; Strandwitz, 2018). Epinephrine (Adrenaline) is aslo produced in the adrenal glands and affects gut motility and blood flow. It's also a key player in the body's 'fight or flight' response and can impact gut processes during stress (Tomé, 2018). While some histamine is produced in the gut, it's also released by mast cells throughout the body. In the gut, histamine plays roles in gastric acid secretion and inflammation (Fiorani et al., 2023). Substance P is a neuropeptide, primarily found in the brain and spinal cord, is involved in pain perception. In the gut, it contributes to pain sensation and inflammation, and can influence bowel motility and fluid secretion (Patel et al., 2020). Vasoactive Intestinal Peptide is not produced in the gut but affects several gastrointestinal functions, including relaxation of smooth muscle, dilation of blood vessels, and stimulation of water and electrolyte secretion in the intestines (Iwasaki et al., 2019). Somatostatin is produced in the hypothalamus and inhibits the release of many other hormones. In the gut, somatostatin slows down the digestive process by inhibiting gastric acid secretion and reducing gastrointestinal blood flow (Tulassay, 1998).

Serotonin and GABA are the two key neurotransmitters produced in the gut. It is hypothesized that they play significant roles in the mood regulation, cognitive functions, development and potential treatment of various neurological and psychiatric conditions. These neurotransmitters influence brain health significantly, suggesting a potential pathway for therapeutic interventions in mental health disorders through gut microbiome modulation. The role of gut-derived neurotransmitters serotonin and GABA, and gut-microbiota in neurological and mental health are illustrated in the below diagram.



The vagus nerve and bloodstream are crucial pathways for gut microbiota to communicate with the brain, influencing mood and behavior through neurotransmitters like serotonin, GABA, and dopamine. Disruptions in these mechanisms are linked to mental health disorders like depression, anxiety, and schizophrenia, emphasizing the importance of the gut-brain axis.

Serotonin: Depression, anxiety, mood regulation
GABA: Stress response, mood disorders, anxiety reduction
Dopamine: Influence on motivation, reward processing and pleasure pathways
Cortisol: Connection to stress levels and anxiety disorders
Glutamate: Excitatory neurotransmitter
Endorphins: Role in pain relief and mood regulation
Acetylcholine: Learning and memory functions
Oxytocin: Impact on social bonding and emotional well-being

Gut microbiota directly influence the production of neurotransmitters like serotonin and GABA, which are crucial for brain health, affecting cognitive function by enhancing memory and learning, and emotional regulation by modulating mood and stress; the gut-brain axis mediates these effects and is implicated in neurological disorders such as depression and anxiety, while a diverse gut microbiota is associated with better cognitive health, with reduced diversity linked to cognitive decline and neurodegenerative diseases.

Fig. 1: The role of gut-derived neurotransmitters and gut-microbiota in neurological and mental health.

PATHWAYS OF THE GUT-BRAIN AXIS

There are four major pathways of the gut-brain axis, the endocrine, humoral/metabolic, immune and neurologic pathways (Carabotti et al., 2015).

Endocrine Pathway

The endocrine pathway includes the communication between the gut and the brain through the release of gut peptides and hormones that impact metabolic homeostasis, food intake, energy expenditure, and glucose regulation (Mithieux, 2018; Wachsmuth et al., 2022). The enteroendocrine cells are specialized neuroendocrine cells of the intestinal epithelium and they sense the luminal environment and release gut peptides such as glucagon-like peptide-1 (GLP-1), cholecystokinin (CCK), peptide YY, neuropeptide Y (NPY), and substance P. These gut peptides enter the bloodstream and directly influence the enteric nervous system, relay signals to the brain, informing the CNS about meal size and composition (Wachsmuth et al., 2022). The gut-derived signals, in response to nutrient influx during a meal, are relayed to the brain, particularly the hypothalamus, which integrates these signals to coordinate the regulation of food intake, energy expenditure, and glucose homeostasis (Wachsmuth et al., 2022). The gut-brain signaling is a bidirectional avenue of communication, with signals from the brain communicating to the gut mainly through the autonomic nervous system (Kasarello et al., 2023; Ullah et al., 2023; Wachsmuth et al., 2022). This endocrine pathway plays a significant role in regulating metabolic homeostasis and influencing behavioral processes, highlighting the intricate connection between the gut and the brain through hormonal signaling. It involves the release of gut peptides and hormones from enteroendocrine cells, influencing metabolic homeostasis and relaying signals to the brain, thereby contributing to the bidirectional communication between the gut and the brain. The gut microbiota can regulate serotonin, thereby affecting the CNS physiology and inflammation and influencing the gut-brain axis. The presence of gut microbiota and their metabolites in the gastrointestinal tract influences the local mucosal system and affects the gut-brain axis through humoral pathways (Foster et al., 2021).

Assessing the luminal environment, enteroendocrine cells in the gut release gut peptides including cholecystokinin and GLP-1, which affect metabolic homeostasis and transmit signals to the brain (Wachsmuth et al., 2022). A further indication of the complex role that serotonin plays in the microbiota-gut-brain axis is the ability of the gut microbiota to influence the metabolism of tryptophan, which is the precursor to serotonin (S. M. O'Mahony et al., 2015). Enteric nervous system, autonomic nervous system, CNS, and hypothalamic-pituitary-adrenal axis are all parts of this bidirectional communication network that enables the brain to control intestinal processes and the gut to influence mood, cognition, and mental health (Carabotti et al., 2015).

Ovarian hormones and their metabolites operate on the GABAergic system, altering its activity during periods of hormonal transition. Inhibitory neurotransmitter, GABA, is trafficked by the GABA system. Its functional effects are explored during key hormonal transition periods, including puberty, the ovarian cycle, pregnancy, the postpartum period, and reproductive ageing. Estradiol, progesterone, and allopregnanolone fluctuations cause the brain to respond accordingly, which leads to increased plasticity during times of hormonal fluctuations. During this time, the GABA system must adapt in order to preserve the balance between excitatory and inhibitory signals (Gilfarb & Leuner, 2022).

Humoral or Metabolic Pathway

The humoral or the metabolic pathway plays a significant role in energy and glucose homeostasis. During a meal, the gut provides crucial information to the brain regarding incoming nutrients, and signals originating from the gut in response to nutrient influx are relayed to the brain, informing the CNS about meal size and composition (Wachsmuth et al., 2022). This pathway encompasses the communication between the gastrointestinal tract and the brain, involving various signaling mechanisms, including gut peptides, hormones, and neural pathways (Makris et al., 2021; Wachsmuth et al., 2022). The gut-brain axis involves different pathways such as the autonomic and enteric nervous system, the endocrine system and the gut microbiota and its metabolites all of which contribute to the regulation of metabolic homeostasis and energy and glucose metabolism (Makris et al., 2021; Rutsch et al., 2020; Wachsmuth et al., 2022). Serotonin and GABA, through their imperative association with the gut-brain axis, may be effective in the treatment of gut disorders

like IBS, IBD and brain disorders like depression, anxiety, schizophrenia, Alzheimer's and Parkinson as well. They involve and govern the pathophysiology of the gastrointestinal and neurological systems, affecting blood flow regulation, intestinal motility, nutrient absorption, the gastrointestinal immune system, and the microbiota and interrelated neural signaling that administer the metabolic pathways (M. Chen et al., 2022).

Through humoral pathways, serotonin influences immune cell regulation, immune cell activation, cell migration, cytokine release, and responses to microbial infection, all of which have an impact on the gut-brain axis (Layunta et al., 2021). Neuroactive compounds like serotonin, which act on the gut-brain axis and affect mood, cognition, and the control of gastrointestinal homeostasis, can be produced and delivered by the gut bacteria. Another way that the gut-brain axis influences brain physiology and pathology is through the production of cytokine-carrying exosomes, which are triggered when serotonin binds to 5-HT receptors on microglia (Rutsch et al., 2020).

IBS, a disorder involving the gut-brain axis that affects blood flow control, intestinal motility, nutritional absorption, the gastrointestinal immune system, and the microbiota, may be effectively treated with GABA and its analogues (Carabotti et al., 2015). Neuroactive chemicals like GABA, which impact mood, mood-brain axis response, and gastrointestinal homeostasis management, can be produced and delivered by the gut bacteria. The immune system, tryptophan metabolism, the VN, and humoral signalling pathways are just a few of the channels via which the microbiota and the brain communicate (Appleton, 2018; Cryan et al., 2019; Mazzoli & Pessione, 2016).

Immunological Pathway

The gut microbiota can influence brain-related functions, like stimulating the production of immune agents, such as inflammatory mediators and cytokines, that target the CNS and ENS (Ullah et al., 2023; Wood & Galligan, 2004). This interaction involves various mechanisms, including cytokines, short-chain fatty acids (SCFAs), and microbial metabolites, conveying the intricate relationship between the immune system and the gut-brain axis (Makris et al., 2021; Ullah et al., 2023). During dysbiosis, these pathways are dysregulated and associated with altered permeability of the blood-brain barrier and neuroinflammation (Rutsch et al., 2020). Another way that the gut-brain axis influences brain physiology and pathology is through the production of cytokine-carrying exosomes, which are triggered when serotonin binds to 5-HT receptors on microglia. Diseases affecting the CNS and other distal organs are linked to gut microbial change or dysbiosis (Foster et al., 2021). Immunological cell activation, cytokine release, cell migration, and responses to microbial infection are among the central immunological processes that are impacted by GABA receptor signalling. Immune system disorders and inflammatory diseases such Type1 diabetes, Rheumatoid arthritis and cancer cell metastasis are linked to GABA signalling. GABA functions as an intercellular signalling molecule in the immune system and in interactions between microbes and hosts, demonstrating conserved GABA signalling across a wide variety of mammalian cells and immune system function diversification (Bhandage & Barragan, 2021).

Neurological Pathway

Molecules such as GABA, serotonin, melatonin, histamine, and acetylcholine that can function as local neurotransmitters are directly produced by neurologic regulation of afferent sensory nerves. This pathway also produces biologically active versions of catecholamines in the gut lumen (Mayer et al., 2014). In the stomach, the autonomic nervous system also affects immune system activation. For instance, it directly affects mast cell and macrophage responses to luminal bacteria. Furthermore, it seems that appropriate gut intrinsic primary afferent neuron excitability depends on the gut microbiota (Iannone et al., 2019; McVey Neufeld et al., 2013). The ENS is a vast network of neurons embedded in the lining of the gastrointestinal tract. It contains as many neurons as the spinal cord and is capable of operating independently of the CNS, but it also communicates extensively with it. It controls various gut functions, including peristalsis, secretion of digestive enzymes, and blood flow regulation in the gut. The most significant component of the gut-brain neurological pathway is the VN, one of the largest nerves connecting the brain to the rest of the body. It runs from the brainstem down to the abdomen, innervating various organs, including the heart, lungs, and digestive tract. This nerve acts in a two-way communication system and sends sensory information from the gut to the brain, including signals

about the state of the gastrointestinal tract, the presence of food, and gut microbiome activity. Conversely, it transmits information from the brain to the gut, influencing digestive processes and gut motility also involving neurotransmitters such as serotonin and GABA. Serotonin is primarily produced in the gut and affects brain functions including mood and emotions, through the gut-brain axis. Other signaling molecules, such as hormones and cytokines, are also involved in this communication (Appleton, 2018; McVey Neufeld et al., 2013; Ullah et al., 2023). GABA functions as the primary inhibitory neurotransmitter in the CNS, reducing neuronal excitability by inhibiting nerve transmission. GABAergic neurons are located in various brain regions, including the hippocampus, thalamus, basal ganglia, hypothalamus, and brainstem. It is involved in regulating ion channels, hyperpolarizing the cell and inhibiting the transmission of action potentials (Appleton, 2018; Mazzoli & Pessione, 2016). GABA acts as an inhibitory neurotransmitter in the adult CNS, but during embryonic development, it acts as an excitatory neurotransmitter. It is involved in modulating ion channels, hyperpolarizing the cell, and inhibiting the transmission of action potentials (Allen et al., 2023; Jewett & Sharma, 2023).

SEROTONIN

Serotonin, also referred to as 5-hydroxytryptamine (5-HT), is a monoamine inhibitory neurotransmitter, that helps regulate mood, behavior and sleep. It decreases the chances of the target cell taking action (Coleman et al., 2019). About 90-95% of the body's serotonin is synthesized in the enterochromaffin cells of the gastrointestinal tract and the remaining 5% is found in the brain (Yaghoubfar et al., 2020). It plays a crucial role in regulating intestinal movements and helping in digestion and absorption. The serotonin released in the gut can act locally on serotonin receptors, influencing gut motility, secretion, and vasodilation. It is crucial for mood regulation and emotional well-being. Low levels of serotonin are often linked with conditions like depression and anxiety disorders. It also influences other brain functions, such as sleep, appetite, and cognitive processes like memory and learning. In the treatment of psychiatric disorders, many antidepressant medications, like Selective Serotonin Reuptake Inhibitors (SSRIs), work by increasing serotonin levels in the brain, helping alleviate symptoms of depression and anxiety. Studies indicate a correlation between gut-derived serotonin levels and mental health disorders. Altered serotonin signaling in the gut can influence CNS activity, potentially contributing to the pathophysiology of conditions such as IBS, depression, and anxiety. Interactions between the microbiota and the serotonergic system in the gut play a pivotal role in the pathogenesis of gut disorders through the serotonin-gut microbiota axis. Through neurological mechanisms involving the ENS and the CNS, the intestinal microbiota can impact the concentration of serotonin in the gastrointestinal tract and host serotonergic neurotransmission in the gut-brain axis. Dysbiosis can cause deregulation of these pathways and is linked to neuroinflammation and changed blood-brain barrier permeability (Yaghoubfar et al., 2020).

The gut microbes have an impact on tryptophan metabolism and that the serotonergic system, working as a key regulator of this process. There is also a significant overlap between behaviours that depend on intact serotonergic neurotransmission and those that are impacted by the gut flora. It is possible that the growing serotonergic system would be susceptible to varied patterns of microbial colonisation before a stable adult-like gut microbiota emerges. On the opposite end of the spectrum, age-related serotonin-related health issues may be determined by the diminished stability and variety of the gut microbiota. The gut microbiota's capacity to regulate host tryptophan metabolism via the kynurenine pathway, which lowers the fraction of tryptophan available for serotonin synthesis and this increases the production of neuroactive metabolites. The immune system and the stress response, two systems that support the brain-gut axis, are the enzymes of this pathway. Localised changes in serotonin concentrations can affect neuronal processes in the gastrointestinal system, which can then convey signals along the brain-gut axis framework to affect CNS neurotransmission. Serotonin-related brain-gut axis illnesses may benefit from therapeutic manipulation of the gut flora (S. M. O’Mahony et al., 2015).

An essential amino acid that needs to be included in the diet is tryptophan (Le Floc’h et al., 2011). It can cross the blood-brain barrier via the major amino acid transporter after being absorbed from the stomach and become available in the circulation, where it exists in both a free and albumin-bound fraction (Fernstrom & Fernstrom, 2006) and can contribute to serotonin production in the CNS (Ruddick et al., 2006). The majority of serotonin is

found in the gut, where enterochromaffin cells (ECs) of the gastrointestinal tract and enteric neurons synthesise it from tryptophan (Mawe & Hoffman, 2013; Spiller, 2008). Tryptophan is a precursor to several important molecules, including serotonin. The kynurenine pathway is a major route of tryptophan metabolism, accounting for over 90% of its degradation. In this pathway, tryptophan is converted into kynurenine and subsequently into several metabolites, some of which can cross the blood-brain barrier and have neuroactive properties. The balance between the serotonin and kynurenine pathways is crucial, as alterations are associated with various mental health disorders, including depression and anxiety. Factors like stress, inflammation, and immune activation can shift tryptophan metabolism towards the kynurenine pathway, impacting mental health (Braidy et al., 2009; Schwarcz et al., 2012). The balance between the serotonin and kynurenine pathways of tryptophan metabolism is a complex process and imbalances are linked to various psychiatric and neurological disorders. For instance, a shift towards the kynurenine pathway and away from serotonin production is associated with increased risk of depression, anxiety, and other mood disorders. Researchers are exploring ways to therapeutically modulate these pathways to treat such conditions (Giada Mondanelli & Claudia Volpi, n.d.; Haq et al., 2021; S. M. O'Mahony et al., 2015; Yang et al., 2013).

Direct gut-microbiome regulation of tryptophan metabolism and serotonin synthesis

Tryptophan can also be directly utilised by the gut flora, which may restrict the host's access to it. Apart from the prerequisites for bacterial development, some bacterial strains have the enzyme tryptophanase, which converts tryptophan to indole (J.-H. Lee & Lee, 2010; G. Li & Young, 2013). For instance, the enzymatic ability of Bacteroides fragilis has recently been connected to gastrointestinal anomalies in autism spectrum disorders (Hsiao, 2013). Although the direct physiological importance of tryptophan-to-indole 3-acetic acid (IAA) synthesis is not fully known, it is crucial to the physiology of bacteria and plant-microbe interactions, where it can have both helpful and negative consequences (Lambrecht et al., 2000). SSRIs and other serotonergic medications given to the host can also affect some microbes, primarily gram-positive bacteria (Munoz-Bellido et al., 2000). In addition to the dietary supply of this necessary amino acid, the balance between bacterial tryptophan utilisation and metabolism, tryptophan synthesis, serotonin production, and even the bacterial response to exogenous elevations in serotonin likely plays a significant role in determining the host's local gastrointestinal and circulating tryptophan availability. These together control serotonin production, which may have effects on CNS and ENS neurotransmission.

Serotonergic System and the Gut-Brain Axis Development

The concept that 5-HT may function as a growth regulator in specific developmental events for both enteric and CNS neurotransmission has been generated by the synthesis of 5-HT, the expression of its receptors in embryonic development and the fetus's maternal and placental sources (Bonnin & Levitt, 2011). Target cells and organs can be affected by the serotonergic system in both the prenatal and postnatal stages of life (Nasyrova et al., 2009). Hormonal, immunological, and neurological pathways are among the gut-brain axis components that develop and mature during pregnancy and the postnatal period, with some of these components not fully established until late adolescence (Clarke, O'Mahony, et al., 2014). There is a developmental overlap with the potential for the gut-brain axis to influence the serotonergic system and vice versa because the serotonergic system acts at both terminals of this axis and is not fully mature at birth.

The development of the CNS in humans starts before mid-gestation in the fetus and continues evolving until puberty (Levitt, 2003), making it sensitive to both genetic and environmental influences during early life. During this period, the brain undergoes rapid changes, which include forming synaptic connections and developing the blood-brain barrier. Before these developments, neurons function like secretory cells, and the brain acts as an early endocrine organ, releasing substances that influence not just its own development but also the growth of other organs, including the gastrointestinal tract (Ugrumov, 2010). Serotonin (5-HT) is a key signaling molecule in this process, crucial for the development of various bodily targets (Munoz-Bellido et al., 2000). Studies have shown that a lack of serotonin in the CNS, as observed in Tph2 knockout mice, can lead to reduced body growth and improper brain wiring, potentially leading to neurodevelopmental disorders. The

sequence of CNS development is broadly similar across different species, but the specific timelines vary (Rice & Barone, 2000), creating different periods of vulnerability. For humans, significant brain growth occurs around birth, whereas, in rodents, this peak is on the seventh postnatal day (Dobbing & Sands, 1973). Despite the Blood-Brain Barrier (BBB) being functional at birth, the developing brain's cerebral vasculature remains fragile, making the neonatal brain more susceptible to circulating toxins than in adulthood (Saunders et al., 2012). This vulnerability is especially crucial considering the variety of new molecules an infant is exposed to after birth and during different nutritional stages. Many of these molecules can be directly or indirectly linked to the metabolic activities of gut microbes, highlighting the intricate relationship between the gut microbiome and early brain development (Clarke, Stilling, et al., 2014; MacFabe, 2012).

The central serotonergic system, originating in the brainstem's raphe nuclei, influences key physiological processes such as mood, sleep, and behavior (Lucki, 1998). Serotonin (5-HT) regulation in the brain changes with age, showing age-dependent adaptations. Serotonin neurons are among the first to develop in the CNS, with serotonin uptake in the developing brain higher than in adults. In rats, the serotonin transporter (SERT) is present from early embryonic stages, with serotonin uptake patterns evolving throughout development. In humans, an increase in SERT binding is observed from ages 3 to 18, followed by a gradual decrease over the decades (Makkonen et al., 2008; Yamamoto et al., 2002). The development of serotonin neurons is complex, involving specific subsets with distinct projections and developmental requirements (Kiyasova & Gaspar, 2011).

Gut microbiota's influence on behavior and central functions suggests a role in the development of the central serotonin system. Studies in germ-free mice indicate that early gut bacteria are crucial for the proper development of serotonergic systems, with these mice displaying changes in serotonin receptors and altered pain responses (Amaral et al., 2008). This research highlights the gut's role in normal pain responses and serotonergic system development in adulthood. Despite relatively stable serotonin levels in the human brain with aging, there is a notable reduction in serotonin receptors over the lifespan (Morgan, 1987).

Serotonin (5-HT) released from enterochromaffin cells in the gut plays a vital role in various gastrointestinal functions such as secretion, peristalsis, vasodilation, and the perception of pain and nausea, primarily through the activation of 5-HT receptors. These receptors are located on both intrinsic and extrinsic afferent nerve fibers. The development of the peripheral serotonergic system begins early in rats at around embryonic day 15 (E15), beginning to produce serotonin at this stage (Nasyrova et al., 2009). By E21, the concentration of 5-HT in the rat gut is similar to that in adult rats, and this level continues to rise as birth approaches, following a similar trajectory into postnatal life (Branchek & Gershon, 1989). Interestingly, once the blood-brain barrier forms in rats (around postnatal days 4–16), there's a notable increase in gut serotonin, suggesting a compensatory mechanism in response to the reduced serotonin supply from the brain. In neonatal guinea pigs, an immature clearance mechanism for serotonin is observed, characterized by low expression of the SERT and slow serotonin turnover. As SERT expression increases, serotonin levels in the gut decrease, indicating a reduction in serotonergic modulation of the developing gastrointestinal tract (Zhao et al., 2011). Given the studied interactions between the gut's immune and microbiota systems and their changes with aging, it's plausible that the 5-HT system within the gastrointestinal system also undergoes changes over time, reflecting the intricate interplay between these systems.

There is a significant overlap in the physiological and behavioral impacts of gut microbiota, tryptophan metabolism, and the serotonergic system. Anxiety and its relation to gut microbiota is complex and any alterations in gut microbiota can influence anxiety-related behaviors, which are modifiable by changing the microbiota. The development of anxiety disorders is closely associated with changes in the serotonergic system, suggesting a connection with gut microbiota composition. SSRIs, which target the serotonergic system are effective in treating anxiety, indicating the potential for microbiota-mediated modulation of serotonergic pathways in treating anxiety. In depression patients, alterations in gut microbiota have been observed, suggesting a link between gut health and depressive states (Naseribafrouei et al., 2014; O'Connor

et al., 2009). Probiotic strains like L. rhamnosus and B. infantis show promise in alleviating depression symptoms, both in animal models and in humans. Antibiotics like minocycline, impacting gut microbiota, have been found to have antidepressant effects, possibly through neuroprotection and anti-inflammatory actions (Ferreira Mello et al., 2013; Miyaoka et al., 2012). More research is needed to understand the specific interactions between gut microbiota and the serotonergic system in mental health disorders, especially at the species level of the microbiota.

The gut microbiota plays a critical role in pain signaling from the gastrointestinal tract, extending its influence beyond the gut (L. O'Mahony et al., 2005). A complete and balanced microbial community is necessary for the proper development of pain signaling pathways in the body (Amaral et al., 2008). Consumption of L. casei Shirota significantly improves gastrointestinal symptoms, including abdominal pain, in Parkinson's disease (PD) patients (Cassani et al., 2011). Microbial colonization in early life is crucial for essential gastrointestinal functions, and disruptions during this period can adversely affect pain pathway development in adulthood. Disruption with C. jejuni activates brain regions processing gastrointestinal sensory information, indicating a direct link between gut microbiota and brain function (Gaykema et al., 2004). L. acidophilus modulates intestinal pain through opioid and cannabinoid receptors, offering potential therapeutic pathways. Probiotic treatments have been effective in reducing IBS symptoms in patients, suggesting a link between gut health and visceral pain management (Clarke et al., 2012). While these studies indicate potential modulation of visceral pain through the serotonergic system and the gut microbiome, the exact relationship and overlap between these two systems require further investigation.

Serotonergic interrelation between the Hypothalamic-Pituitary-Adrenal axis (HPA) and the Gut-Brain axis

Serotonin acts as an ideal connectection between the gut-brain-microbiota axis, with microbiota regulating tryptophan metabolism involved in serotonin production, serotonin influencing both gastro-intestinal physiology and the processes of CNS, and crucially serotonin receptors playing a pivotal role in the HPA axis. The neuroendocrine HPA axis controls how the body reacts to stress and interacts intricately with the dopamine, noradrenergic, and serotonergic systems in the brain (Pompili et al., 2010). Through activation of the serotonin 2C receptor, serotonin activates the HPA axis. Dysregulation of the serotonergic system is linked to abnormalities in the HPA axis in response to elevated stress levels (Heisler et al., 2007). Additionally, abnormalities in the functioning of HPA axis can lead to long-term changes in the synthesis of neuropeptides and neurotransmitters in the CNS. The HPA axis is a complex system of neuroendocrine pathways and feedback loops that maintain physiological homeostasis. Serotonin also influences adrenocortical cells and is involved in the regulation of the brain-pituitary-adrenal axis (Sheng et al., 2021).

HPA axis controls the release of cortisol, which impacts the gut microbiota and brain activity. By controlling gut hormones, neuropeptides, and cytokines, which can either stimulate or inhibit HPA axis activity, the ENS can affect the HPA axis. On the other hand, the HPA axis can influence the ENS by modifying the secretion and motility of the gut as well as the activity of glial cells and enteric neurons. This two-way communication implies that the gut-brain axis is regulated by the ENS and HPA axis, which are closely related (Misiak et al., 2020; Rusch et al., 2023; Tan, 2023). Therefore, the HPA axis and GBA are critically interconnected through complex interactions involving different neural, immune, and endocrine pathways, and they regulate stress responses, gut function, and brain health (Rusch et al., 2023).

Therapeutic targeting of the gut microbiome in pertinence to the serotonergic system

Some bacteria, including Candida, Streptococcus, Escherichia, and Enterococcus, can produce 5-HT, potentially delivering this neurotransmitter to the gastrointestinal system. Probiotic bacteria produce neuroactive substances like GABA and 5-HT, influencing the brain-gut-microbiome axis and displaying anxiolytic and antidepressant-like activities (Desbonnet et al., 2008; Dinan et al., 2013).

GABA (GAMMA-AMINOBUTYRIC ACID)

GABA serves as the brain's primary inhibitory neurotransmitter and it serves as check point to the brain's excitability and it decreases a neuron cell's capacity to produce, receive, and communicate chemically with other nerve cells (Sigel & Steinmann,

2012). It plays a pivotal role in reducing neuronal excitability and is therefore important for relaxation, stress reduction, and overall mental calmness. Low levels of GABA are associated with conditions like anxiety disorders, panic attacks, and certain types of epilepsy. Certain drugs and supplements are used in treatment with with the objective of raising GABA activity to assist reduce anxiety and elevate mood. In order for the brain to operate effectively, GABA works together with glutamate, an excitatory neurotransmitter, and maintains a precise equilibrium. It involves in regulation of the balance between inhibitory and excitatory neurotransmitters for proper brain function. Disregulation in GABA signaling is involved in various neurologic and psychiatric conditions. Though glutamate is the precursor of GABA, they both play opposite roles in the nervous system, GABA as an inhibitory neurotransmitter and glutamate as an excitatory neurotransmitter (Ting Wong et al., 2003). GABA and glutamate imbalances have been linked to a number of illnesses, as was covered in Clinical Significance.Investigation and thereby modulation of GABA signaling is the basis of many pharmacologic treatments in neurology, psychiatry, and anesthesia (Jewett & Sharma, 2023; Kondziella, 2017; Sigel & Steinmann, 2012). Gabapentin, an analogue of GABA, is a drug used for the treatment of seizures and neuropathic pain. It interacts with GABA receptors and has been shown to increase GABA concentration in the brain, contributing to its therapeutic effects and are commonly used as anticonvulsants, sedatives, and anxiolytics (Allen et al., 2023; Cai et al., 2012; Jewett & Sharma, 2023).

GABA is associated to the gut-brain axis and engages in intricate bidirectional communication between the gut and the brain. GABAergic signaling in the gut-brain axis is significant in interkingdom signaling between bacteria, fungi, invertebrates, plants and mammals. Understanding GABA-mediated communication in the gut-brain axis requires an understanding of GABA signalling and metabolism within bacterial communities (Quillin et al., 2021). It has been discovered that certain gut microbiota like Bifidobacterium adolescentis generate GABA, which affects the gut-brain axis response (Duranti et al., 2020). Through bidirectional connection between the central and enteric neural systems, the gut-brain axis connects the brain's emotional and cognitive centres to peripheral intestinal activities (Carabotti et al., 2015). The hippocampus, thalamus, basal ganglia, hypothalamus, and brainstem are regions that contain GABAergic neurons. For optimal cell membrane stability and neurologic function, there must be a balance between excitatory neuronal transmission via glutamate and inhibitory neuronal transmission via GABA. Furthermore, it has been demonstrated that the gut microbiota's GABA and glutamate signalling modulates gut and brain processes, influencing mood, cognitive abilities, and the control of gastrointestinal homeostasis (Mazzoli & Pessione, 2016).

GABA Receptors

GABA receptors are inhibitory receptors that react and get activated when neurotransmitter GABA enters the post-synaptic nerve terminal. There are two main types of GABA receptors, GABAa and GABAb, each type playing a distinct role in neural signaling (Sigel & Steinmann, 2012). The GABAa receptors are classified as ligand-gated ion channels and are involved in fast synaptic inhibition. When GABA binds to these receptors, they allow chloride ions to enter the cell, reducing its resting potential and producing an inhibitory effect. They are found throughout the CNS, with particularly high concentrations in the limbic system and the retina (Sigel & Steinmann, 2012). The GABAb receptors are G-protein coupled receptors that contribute to slow synaptic inhibition. Binding of GABA to GABAb receptors increases potassium conductance and activates adenylyl cyclase, which inhibits calcium entry and reduces the release of other neurotransmitters. These receptors are predominantly located in the thalamic pathways and the cerebral cortex. While GABAa receptors are involved in immediate response by allowing chloride ions into cells, GABAb receptors work more slowly by affecting potassium conductance and neurotransmitter release.

Although GABA is the main inhibitory neurotransmitter in the adult CNS, it functions as an excitatory neurotransmitter during the development of the embryo. It contributes to the growth of neural progenitor cells and is believed to be the first neurotransmitter to become active in the developing brain. GABA reduced proliferation in the subventricular zone but enhanced it in the ventricular regions, increasing the size of neural progenitor cells (D. D. Wang & Kriegstein, 2009; C. Wu & Sun, 2015).

GABA and the Gut-Brain axis

GABA plays a significant role in the gut-brain axis. GABA is not only produced in the brain but also in the gut. Certain gut bacteria can synthesize GABA from glutamate. This production of GABA in the gut can influence local gut activities and potentially signal to the brain. The composition of the gut microbiota can influence GABA levels too. Some microbial strains are capable of producing GABA, which can affect gut motility and integrity, as well as influence the gut-brain signaling. Being a key inhibitory neurotransmitter in the brain, its role in the gut-brain axis is to help regulate stress responses and mood, as alterations in GABA signaling have been linked to anxiety and depression. Changes in gut-derived GABA levels can impact the CNS. For example, altered GABA signaling due to gut microbiota changes has been associated with various CNS disorders, including anxiety, depression, and autism spectrum disorders. Modifying gut microbiota to influence GABA production could be a therapeutic strategy for neurological and psychiatric disorders. GABA can also interact with the gut's immune system, influencing inflammatory responses, which in turn affect gut and brain health and their physiological processes.

INTERPLAY BETWEEN THE GUT-BRAIN AXIS AND IMMUNE SYSTEM

The gut-brain axis regulates immune system and gastrointestinal processes like peristalsis and mucus formation. The gut microbiome's composition is influenced by stress, and the host's level of stress is influenced by the gut microbiota's and the CNS's reciprocal communication. In major depressive disorders (MDD), bipolar, anxiety, schizophrenia, psychosis, neurodegenerative illnesses, autism spectrum disorders, mood, cognitive, and behavioural changes are significantly impacted by the composition of the gut microbiota. It is critical to comprehend the precise functions that the gut microbiota plays in fostering mental health and the development of suitable therapies (Dinan & Cryan, 2017; Khan et al., 2022; Ullah et al., 2023). The symbiotic link between the host and microbiota has been maintained by the human immune system throughout evolution, and any disruption of this dynamic immunological-microbial interaction has a significant negative impact on human health.

Inflammasome signaling pathway

An innate immune signalling complex called the inflammasome is triggered by a variety of endogenous and microbial danger signals. It is composed of a sensor protein, inflammatory caspases, and in some cases, an adapter protein connecting the two. The inflammasome activation recruits apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and the cysteine protease caspase-1 through caspase activation and recruitment domain (CARD) to induce the proteolytic cleavage of pro-caspase-1 to generate mature and active caspase 1, which further processes pro-IL-1β and pro-IL-18 to the final production of bioactive IL-1β and IL-18 proteins (Franchi et al., 2009; D. Li & Wu, 2021; Makoni & Nichols, 2021). The NLRP3 inflammasome is a critical component of the innate immune system that mediates caspase-1 activation and the secretion of proinflammatory cytokines IL-1β/IL-18 in response to microbial infection and cellular damage (Kelley et al., 2019). The gut microbiota can influence inflammasome signaling, and the interplay between the gut microbiome and inflammasome may impact the regulation of neurotransmitters and emotional distress (Zheng et al., 2020). Inflammasome-mediated dysbiosis impacts a number of diseases, including major depressive disorders, which are often associated with activated inflammasome and elevated levels of proinflammatory cytokines, such as IL-1β, IL-6, and IL-18 proteins. Inhibition of caspase-1 attenuates inflammation and anxiety-like behaviors and modulates the composition of gut microbiota (Hentze et al., 2003). These studies collectively suggest that gut microbiota influence anxiety- and depression-induced behaviours by modulating inflammatory response through inflammasome signalling.

Type I interferon signaling pathway

Type I interferon (IFN-I) is a cytokine that plays a crucial role in innate and adaptive immunity and maintaining host homeostasis. IFN-I can have both positive and negative immunomodulatory functions in various human conditions (Steed et al., 2017). IFN-I also affects the composition of gut microbial communities, suggesting a bidirectional interaction between microbiota and IFN-I signaling (Giles & Stagg, 2017).

NF-κB signaling pathway

Pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) are molecules that are often released by damaged cells or found in pathogens. Pattern recognition receptors (PRRs) are proteins expressed by cells in the innate immune system that recognise these molecules. PRRs are specifically positioned within the cell; they are found at the surface to identify external pathogens like bacteria or fungi, and inside endosomes and the cellular matrix to identify viruses that invade the cell from within. They have the ability to attach to microorganisms as secreted proteins, initiate phagocytic responses, and activate pro-inflammatory signalling pathways. These receptors are essential for the innate immune response because they trigger immune cell activation and cell death pathways in response to pathogenic threats (Meng et al., 2015).

Immune cells in CNS

PRRs are proteins expressed by cells in the innate immune system that recognize molecules frequently found in pathogens, known as PAMPs, or molecules released by damaged cells, known as DAMPs. PRRs are strategically localized in the cell, present at the cell surface to recognize extracellular pathogens such as bacteria or fungi, and within the endosomes and cellular matrix to detect intracellular invading viruses. They are involved in activating pro-inflammatory signaling pathways, stimulating phagocytic responses, and binding to micro-organisms as secreted proteins. Gut microbiota can promote the development of different subsets of CD4+ T helper cells, such as Th1, Th2, Th17, and Treg cells, through antigen stimulation and activation of immune signaling pathways (Arpaia et al., 2013; Furusawa et al., 2013; Haghikia et al., 2016; Kim et al., 2014).

The Blood-Brain Barrier (BBB) and the Vagus Nerve (VN)

A selective barrier that separates the brain from the circulatory system, the BBB acts as a conduit for a variety of messages from the gut to the brain. BBB-permeable substances typically contain lipid-soluble characteristics, a low molecular weight, and the ability to alter brain physiology. According to studies, these features are shown by metabolic products in the intestines, allowing them unrestricted passage through the BBB to modify brain function (Banks, 2009; Bourassa et al., 2016). The parasympathetic nervous system includes the VN, which serves as a major neural conduit for gut bacteria and the CNS (Bravo et al., 2011; Forsythe et al., 2014). VN actively participates in the bidirectional interactions between gut microbiota-brain to maintain homeostasis in both the cerebrum and intestine. Dysfunction of the VN may cause CNS dysfunction or gastrointestinal pathologies (Bonaz et al., 2017a, 2017b; Travagli & Anselmi, 2016). The BBB is crucial for safeguarding the brain and keeping poisons and germs out of the CNS. The integrity of the blood-brain barrier can be influenced by gut microorganisms, and specific microbiota components can govern the transfer of additional microbial signals from the gut to the brain. Since the VN is essential to this communication, treating CNS illnesses by focusing therapies on the VN may be a beneficial approach (Tang et al., 2020).

CLINICAL IMPLICATIONS OF SEROTONIN AND GABA IN PSYCHIATRIC DISORDERS THROUGH GUT-BRAIN AXIS

The gut-brain axis is a key player in neurological diseases, involving the microbiota, gut and brain (Boris & Vanessa, 2023). This communication is bidirectional, utilizing both neural and humoral pathways (Berthoud et al., 2021). The enteric microbiota, including commensal and pathogenic organisms, play a crucial role in this interaction, influencing gut function and the nervous system (Rhee et al., 2009). A component of the microbiota-neuron axis is NF-κB signalling. Dysbiosis cause elevated NF-κB activation and TNF-α production in animal models that generate memory impairment. Conversely, restoring the microbiota composition reduces neuroinflammation in the hippocampus and ameliorates associated symptoms (Jang et al., 2018; Ma et al., 2019).

The gut-brain axis links emotional and cognitive centers of the brain with peripheral intestinal functions. It primarily serves to link the autonomic nervous system's sympathetic and parasympathetic branches, which are responsible for sending afferent and efferent neural impulses from the gut to the brain, respectively. Coordination of adaptive responses to stress, such as limbic system activation of memory and affective centres in the brain, is facilitated by the HPA axis. The gut microbiota is essential to the GBA because it regulates gastrointestinal homeostasis, mood, and cognitive

processes via a variety of signalling pathways, including humoral, neuronal, endocrine, and immunological ones (S. M. O'Mahony et al., 2015; Socała et al., 2021). Through a variety of neurological routes, such as the VN, the ENS, and the activity of neurotransmitters within the gastrointestinal tract, the neurotransmitters serotonin and GABA, which are inhibitory neurotransmitters, play critical roles in the GBA, influencing mood, thought and mental health (Appleton, 2018; S. M. O'Mahony et al., 2015). Changes in serotonin signalling have been linked to modifications in the gut flora, which can affect mental health conditions and emotional discomfort (Appleton, 2018; Bornstein, 2012; Carabotti et al., 2015). Expressed in the enteric and CNS, serotonin receptors, including 5-HT3 receptors, are ligand-gated ion channels that mediate excitatory postsynaptic responses (Carabotti et al., 2015). The control of neurotransmitters and emotional discomfort may be impacted by the interaction between the gut bacteria and serotonin, which can affect serotonin signalling (Bornstein, 2012). Serotonin is one of the neuroactive compounds that the gut microbiota can create and supply. This affects mood, cognitive function, and the maintenance of gastrointestinal homeostasis. It also influences the gut-brain axis response (Appleton, 2018; Lin et al., 2014; Stasi et al., 2019). The mentioned discoveries explain the complex interrelationships among serotonin, gut microbiota, and the gut-brain axis.

Low concentrations of GABA have been associated with various psychiatric illnesses, including generalized anxiety, schizophrenia, autism spectrum disorder, and major depressive disorder. As it is an inhibitory neurotransmitter, decreased GABA levels can lead to anxiety. However, GABAa receptor agonists are not the first-line therapy due to high addiction potential and potentially fatal adverse effects. Valproic acid, a GABA analog, can be used for mood instability due to the enhancement of GABA concentrations (Schür et al., 2016). Low levels of GABA are associated with seizures and epilepsy. Decreased levels of inhibition in the cerebral cortex can lead to seizure activity. GABA agonists, such as Valproic acid, are used for the treatment of seizures. Abrupt withdrawal from medications such as benzodiazepines, a GABAa positive allosteric modulator, can provoke seizures. Additionally, GABA antagonists are pro-convulsant (Dm, 2001). Rare inherited disorders of GABA metabolism include GABA-transaminase deficiency, succinic semialdehyde dehydrogenase deficiency (SSADH), and homocarnosinosis. SSADH is the most common of neurotransmitter deficiencies and presents with a vague phenotype, varying neurological manifestations, and psychiatric illness. GABA is unable to be converted to succinic acid, and gamma-hydroxybutyrate (GHB) accumulates. Elevated concentrations of GABA and GHB are found within serum and urine. Diagnosis can be made with urinary excretion of GABA and increased signaling in the globus pallidus on MRI. Characteristics include expressive language impairment, hypotonia, and seizures. The most common neuropsychiatric problem is sleep disturbance along with other issues like inattention, hyperactivity, and obsessive-compulsive disorder (OCD). There is currently no standard treatment for SSADH deficiency. GABA-transaminase deficiency is an autosomal recessive disorder associated with seizures presenting in the neonatal period, hypotonia, hyperreflexia, severely delayed psychomotor development, and a high-pitched cry. High concentrations of GABA are found in serum and cerebrospinal fluid (Jewett & Sharma, 2023). Seizures and epilepsy are linked to low GABA levels, which have been linked to a number of mental disorders, such as major depressive disorder, autistic spectrum disorder, generalised anxiety, and schizophrenia. Rare inherited abnormalities of GABA metabolism, such as homocarnosinosis, SSADH and GABA-transaminase deficiency, call for greater clinical suspicion. The production and delivery of neuroactive chemicals like GABA by the gut microbiota can impact mood, cognitive abilities, and the maintenance of gastrointestinal homeostasis. This can also influence the gut-brain axis response (Socała et al., 2021).

Summarizing, both serotonin and GABA are produced in the gut and can influence the brain through the gut-brain axis and reciprocally, the gut microbiome can influence the production of these neurotransmitters. Therefore, any changes in gut health, can impact the levels of these neurotransmitters, potentially influencing mental health.

THE GUT-BRAIN AXIS AND NEUROLOGICAL DISORDERS

The Gut-brain axis and the CNS have been known to be involved in a number of psychiatric disorders. Out of the many related disorders, few of them are briefed below.

Parkinson's disease (PD)

PD is a neurodegenerative condition marked by the build-up of α-synuclein in the surviving neurons in the substantia nigra and the loss of dopaminergic neurons in those neurons (Schneider & Alcalay, 2017). According to recent research, during the early stages of the disease, α-synucleinopathy is linked to particular digestive symptoms and may start in the ENS before moving to the CNS (Lebouvier et al., 2009; Natale et al., 2011). Evidence suggests that the evolution of PD may have involved the gut microbiota. Depleting the microbiota in young α-synuclein overexpressing mice may have prevented the development of PD in adulthood (Sampson et al., 2016). It has been demonstrated that microbial metabolites, such as SCFAs, activate immune cells' PRRs and aryl hydrocarbon receptors, which controls immunological responses (Kim, 2018). Inflammasomes, which are high-molecular-weight protein complexes that trigger pro-inflammatory and microbicidal reactions necessary to eradicate or contain infectious organisms, can be formed when PRRs on immune cells are activated (Próchnicki & Latz, 2017). NF-κB signalling has been demonstrated to be regulated by the NLRP6 inflammasome, and changes in succinate and butyrate have been found to significantly boost NF-κB. Changes in the number of specific bacterial species, such as Enterobacteriaceae and Lachnospiraceae, have been connected to the severity of PD symptoms and have been linked to dysbiosis of the gut microbiota. These results imply that the gut microbiota and its metabolites are important players in the pathophysiology of PD and could be targets for the creation of new treatment approaches (Barichella et al., 2019; Scheperjans et al., 2015).

Schizophrenia

The pathogenesis of schizophrenia is unclear, however anomalies in signal transduction networks have been linked to the cognitive illness. Kinases are among the signalling molecules that regulate processes linked to schizophrenia, including neurotransmitter systems, cytoskeletal organisation, and gene expression. Subtle alterations in signalling networks that impact several areas, such as cell metabolism, molecular trafficking, intercellular signalling, and the functional integrity of neurocircuits, may be the cause of schizophrenia (Landek-Salgado et al., 2016; McGuire et al., 2017). Numerous signalling pathways, such as the AKT/GSK3 signalling pathway, DISC1, NRG1, and calcineurin, have been found to be significant in the development of schizophrenia. Because these molecules are functionally related to one another, a disruption in one of their functions may impair the effectiveness and efficiency of signals being transmitted from the cell membrane to the nucleus, which may ultimately lead to the failure of cellular function. Evaluating phosphatase activity and the balance of phosphorylation/dephosphorylation within brain regions and cell types should be a top goal for comprehending cell signalling dysfunction in schizophrenia. While a number of signalling molecules' roles in schizophrenia have been identified with considerable progress, further study is required to completely comprehend the disorder's intricate aetiology (Emamian, 2012; Nicodemus et al., 2010; Sui et al., 2008).

Depression and Anxiety

Comorbid diseases like anxiety and depression are linked to cellular and molecular abnormalities that interact with environmental and genetic variables. An underlying factor in the emergence of anxiety and depressive-like behaviours is stress, which can lead to BBB malfunction marked by leakage and inflammation. Oxidative stress, immune/ inflammatory substrates, and NF-κB signalling are the molecular signalling pathways linked to stress-induced anxiety, depression, and BBB inflammation and leakage. Furthermore, the characterization of the intracellular signalling pathways responsible for stress and depression, as well as the activities of antidepressants, has been completed (Duman & Voleti, 2012; Welcome, 2020, 2020). Furthermore, characterizations of the intracellular signalling pathways underlying stress and depression, as well as the activities of antidepressants, have been made. The pathogenesis and therapy of depression are underpinned by signalling pathways that modulate neurotransmission, molecules involved in endocrine and metabolic cascades, and substrates associated to oxidative stress, immunological response, and inflammation. The deficiencies in brain connection associated with schizophrenia are caused by an imbalance in homeostatic signalling from immune/inflammatory, oxidative stress, endocrine, and metabolic cascades. These results imply that particular signalling molecules and pathways have a role in the aetiology of schizophrenia, depression, and anxiety, and that therapeutic approaches aimed at addressing these

pathways may be successful (Duman & Voleti, 2012; Landek-Salgado et al., 2016).

Autism Spectrum Disorders (ASD)

Repetitive behaviours, narrow interests, and difficulty with social communication are hallmarks of autism spectrum disorders (ASD). ASD is a complicated aetiology that includes immunological, environmental, and genetic components. The pathogenesis of ASD has been linked to dysregulation of the mTOR signalling system, purine signalling pathway, and lipid metabolism (Dai et al., 2023; B. Wang et al., 2022; Yui et al., 2022). Potential therapeutic approaches for ASD related to serotonin and GABA include targeting lipid metabolism like Omega-3 fatty acids such as DHA and EPA have been shown to regulate neuroinflammation and improve behavioral symptoms in ASD patients (Yui et al., 2022). Dysregulation of purine metabolism may be associated with ASD, and targeting this pathway could potentially be a therapeutic strategy, by modulating purine signaling (Dai et al., 2023). mTOR signaling has been activated in ASD patients, and inhibiting this pathway could potentially reduce the release of proinflammatory molecules and alleviate symptoms (B. Wang et al., 2022). Serotonin and GABA are involved in the pathophysiology of ASD and therefore targeting and amnipulating these neurotransmitter systems could potentially improve behavioral and cognitive symptoms. In order to create more potent treatment plans for ASD, future studies should clarify the precise molecular targets and signalling pathways involved in the disorder's pathophysiology (Jiang et al., 2022).

CHALLENGES AND LIMITATIONS IN RESEARCH

There are a number of barriers and determing conditions while examining the complex interaction between the gut-brain-microbiota axis and the serotonergic system. First of all, identifying particular causal links is challenging due to the extreme complexity of this axis and the variety of functions that serotonin plays. The variance in gut microbiota among people introduces an additional level of complexity, making it more difficult to generalise the results to larger groups. Moreover, the majority of present day discoveries come from animal models, and there is still a considerable barrier in applying these discoveries to human physiology.

FUTURE DIRECTIONS AND POTENTIAL THERAPEUTIC APPROACHES

Future research should focus on developing more complex models that accurately reflect human physiology, including longitudinal studies to track changes over time. Advancements in non-invasive imaging and molecular techniques will be crucial in elucidating the precise mechanisms at play within the gut-brain-microbiome axis. Further exploration needs to be invested into how diet, lifestyle, and environmental factors influence this axis that could unlock new preventative and therapeutic strategies. Collaborative efforts across different disciplines will be essential to fully understand the multifaceted interactions within this complex system. Treating neurological and psychiatric disorders may be made more effective by comprehending the ways in which the brain is affected by gut-derived serotonin and GABA. The production of these neurotransmitters may be altered by treatments that target the gut microbiome, such as dietary modifications, probiotics, or prebiotics, which may provide novel approaches to the treatment of mental health conditions. SCFAs, for example, are metabolites produced by the microbiota that may also have neuroprotective properties and influence brain function. For diseases including anxiety, depression, and several neurodevelopmental disorders, this field of study holds great promise. To investigate whether various interventional strategies targeting the gut microbiota could be used in the prevention and treatment of neurological illnesses, as well as to comprehend the molecular mechanisms behind how gut microbiota-associated metabolites impact brain functions, more study is necessary.

CONCLUSION

The importance of the crosstalk between the gut-microbiota and the serotonin, GABA pathways in maintaining homeostasis and how disruption of this balance can contribute to the development of gastrointestinal and CNS disorders can be understood. The modulation of the microbiota-gut-brain axis may be a novel therapeutic approach for the treatment of neuropsychiatric diseases. Tryptophan and the 5-HT system are crucial at all levels of the brain-gut-microbiome axis. Current treatments focusing on direct manipulation of the 5-HT system are only partially effective due to the heterogeneous nature of stress-related brain-gut axis disorders and the diverse functions

of 5-HT. A deeper understanding of the brain-gut-microbiome axis and the tryptophan/5-HT system interaction could lead to more effective therapies. This research area suggests a fundamental connection between gut microbiota and serotonergic signaling with definitive causal relationship in clinical aspects and these are yet to be established. This understanding opens the possibility of targeting gut microbiota as a treatment strategy for serotonin-related and GABA-related gut-brain axis disorders. The blood-brain barrier, which acts as a conduit for a variety of signals from the gut to the brain, can also be impacted by gut bacteria. Treatments for CNS diseases like depression, anxiety, and schizophrenia may benefit from new therapeutic approaches that involve altering the composition of the gut microbiota and the signalling molecules that are produced by it. Further research is required to understand the molecular mechanisms underlying the physiological processes of gut-brain axis and to explore the potential applications of different interventional strategies targeting the gut microbiota in the prevention and treatment of neurological illnesses.

ABBREVIATIONS

5-HT	5-hydroxytryptamine
BBB	Blood-Brain Barrier
CNS	Central nervous system
DAMPs	Damage-associated molecular patterns
ENS	Enteric nervous system
GABA	Gamma-Aminobutyric acid
GHB	Gamma-hydroxybutyrate
GLP-1	Glucagon-like peptide-1
HPA	Hypothalamic-Pituitary-Adrenal axis
IBS	Irritable bowel syndrome
IBD	Inflammatory bowel disease
IFN-I	Type I interferon
PAMPs	Pathogen-associated molecular patterns
PD	Parkinson’s disease
PRRs	Pattern recognition receptors
SCFAs	Short-chain fatty acids
SERT	Serotonin transporter
SSADH	Succinic semialdehyde dehydrogenase deficiency
SSRIs	Selective Serotonin Reuptake Inhibitors

DECLARATIONS

Ethics approval and consent to participate

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Consent for publication

Not applicable

Availability of data and material

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