PERSPECTIVES

The Gut-Brain Connection: Implications for Health

Shawn Manske, ND

***Shawn Manske**, ND, is the Assistant Director of Clinical Education for Biocidin Botanicals, supporting clinical education, research, and product development. He brings experience in both clinical practice and practitioner education to his role. Dr. Manske grew up in Ontario, Canada, and graduated from the Canadian College of Naturopathic Medicine. He has worked in private clinical practice focusing on GI dysfunction, autoimmune disease, and cardiovascular disease. Based in Western New York, Dr. Manske is also an experienced educator in the botanical supplements industry.*
(*Altern Ther Health Med.* 2024;30(4):6-9).

Corresponding author: Shawn Manske, ND
E-mail: drmanske@biocidin.com

Consider this: humans have never existed without a symbiotic relationship with microbes. And the brain has never been without signals from the gut and its resident microbes.[1]

These powerful statements underscore the importance of the connections and interactions between our gastrointestinal (GI) system, the microorganisms that reside there, and our brain and central nervous system (CNS). Understanding how microbes in the gut influence brain health and cognitive function is one of the most exciting areas of research in neuroscience and biological psychiatry today.

Much of this research is focused on the gut-brain axis—an intricate series of neural pathways that carry signals between the enteric nervous system (ENS) of the GI tract and the CNS.[2] This dynamic and bidirectional communication network facilitates a complex coordination of neural, hormonal, and immunological interactions that influence various physiological processes beyond digestive function.

The gut-brain axis plays an important role in regulating mood, metabolism, and immune function and may even influence higher cognitive functions such as memory, learning, and decision-making. Emerging evidence also suggests that disturbances in gut-brain communication may contribute to the pathogenesis of a wide range of neurological and psychological disorders, including depression, anxiety, dementia, and irritable bowel syndrome (IBS).

As we dive deeper into an examination of the gut-brain axis, we'll cover the mechanisms underlying this intricate connection and explore its implications for health and disease.

Neural pathways of the gut-brain axis: understanding the communication network

The gut-brain axis's network of neural pathways connects the CNS, the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic components of the autonomic nervous system, the ENS, and the gut microbiome, coordinating a complex interplay between gut function and brain activity.[3]

The vagus nerve, the longest cranial nerve that extends from the brainstem to the abdomen, is a major pathway for neural communication along the gut-brain axis. Originating in the medulla, it innervates structures in the neck, thorax, and abdomen.[4] The vagus nerve is involved in critical aspects of human physiology, including heart rate, blood pressure, sweating, digestion, and even speaking.[5] It also plays a crucial role in regulating gut motility, secretion, and blood flow through its efferent fibers. Motor signals originating in the brain travel down the vagus nerve to the ENS, modulating GI function and coordinating digestive processes. Sensory (afferent) neurons in the gut mucosa detect conditions such as nutrient availability, gut motility, and microbial metabolites. These neurons transmit these sensory signals to the brainstem, providing the brain with real-time information about gut function and microbial activity. Thus, the vagus nerve is a vital pathway that serves as a direct link between the gut and the brain, conveying sensory information from the gut to the brain and transmitting motor signals from the brain to the gut.[6]

The ENS, consisting of millions of neurons and glial cells organized into interconnected ganglia embedded within the gut wall, supports communication along the vagus nerve. Because it can autonomously control GI tissue dynamics and gut homeostasis without input from the brain or spinal cord, the ENS is sometimes referred to as the "second brain."[7] The vast network of ENS neurons—comprising sensory and motor neurons and interneurons—regulates gut function independently of the CNS. This independence relies on local reflexes that control gut motility, secretion, and blood flow in response to stimuli within the GI tract. These reflexes allow for rapid and coordinated responses to changes in luminal contents, ensuring efficient digestion and absorption of nutrients.[8]

While the ENS operates autonomously, it communicates with the CNS via the vagus nerve and other neural pathways. This bidirectional communication enables the brain to modulate gut function in response to emotional and cognitive cues like stress and arousal.

Neurotransmitters and neuromodulators: mediators of gut-brain communication

The chemical messengers that communicate throughout the gut-brain axis comprise an array of neurotransmitters and neuromodulators that affect synaptic firing and neuronal activity. Studies of these neurotransmitters have mainly revolved around their role in the "fight or flight" response, transmitting signals across a chemical synapse and modulating blood flow throughout the body. However, these compounds can also affect gut motility, nutrient absorption, the GI innate immune system, and the microbiome.[9]

Serotonin, sometimes called the "happy hormone," is mainly synthesized by serotonergic neurons in the raphe nuclei within the CNS. Abnormal expression and function of serotonin in the brain are associated with the pathogenesis of mental health disorders, including depressive and anxiety disorders.[10] Interestingly, approximately 90% of serotonin is synthesized peripherally, mainly by enterochromaffin cells in the intestinal epithelium. There, it regulates gut motility, secretion, and sensation and further acts as a signaling molecule that modulates mood, appetite, and social behavior—highlighting its dual role in gut-brain communication.[11,12]

Gamma-aminobutyric acid (GABA) and glutamate, which are (respectively) the primary inhibitory and excitatory neurotransmitters in the CNS, also play a role in the gut-brain axis. GABAergic and glutamatergic neurons within the ENS modulate gut motility and sensory processing, contributing to the regulation of GI function.[13]

Neuropeptides, such as substance P, vasoactive intestinal peptide, and calcitonin gene-related peptide, are released by enteric neurons and sensory fibers in the gut in response to various stimuli, contributing to neuroimmune interactions, which play an important role in homeostasis in the gut.[14] These neuropeptides act as signaling molecules that mediate pain perception, vasodilation, and immune modulation, influencing gut-brain communication.

Disruption of neural pathways in the gut-brain axis has been implicated in the pathogenesis of various GI and neurological disorders, including IBS, inflammatory bowel disease (IBD), and mood disorders.[15] Altered neural signaling contributes to the development of functional GI disorders, such as IBS, and is characterized by abdominal pain, bloating, and altered bowel habits. These symptoms are the result of visceral hypersensitivity, abnormal gut motility, and altered pain processing.

Inflammation originating in the gut can also impact neural pathways in the gut-brain axis, aggravating symptoms in patients with IBD. This gut-derived inflammation can activate neuroinflammation, which can contribute to the increased visceral pain, fatigue, and mood disturbances commonly reported by individuals with Crohn's disease or ulcerative colitis. Indeed, dysregulation of this axis in patients with IBD has long been associated with mental health conditions such as stress, anxiety, and depression. In some clinical studies, stress, anxiety, and depression have been considered triggers of IBD relapse and clinical deterioration.[16]

Alterations in neurotransmitter signaling, neuroinflammation, and stress-response pathways in the gut-brain axis have been implicated in the pathophysiology of anxiety and depression, as well as Alzheimer disease, dementia, Parkinson disease, autism spectrum disorder, and schizophrenia, highlighting the interconnectedness of gut health and mental well-being.

The gut microbiota—the collection of microorganisms residing in the GI tract—also produces neuroactive metabolites, such as neurotransmitters or their precursors, which can affect the concentrations of either in the brain. This suggests that the neurotransmitter synthesis pathway in the intestine might directly or indirectly affect the brain's neuronal activity and cognitive functions.[17]

Hormone signaling and gut peptides in the gut-brain axis

Recent research on the central role of hormone signaling and gut peptides in the gut-brain axis has provided insight into the intricate communication between the GI system and the CNS. Gut hormones, produced in response to nutrient-related signals and feeding behavior, are secreted by enteroendocrine cells (EECs) and have a wide range of targets, including the CNS.[18] Most gut hormones mainly regulate appetite and food intake. However, they can also regulate other physiological processes, such as inflammation, which is linked to brain disorders including anxiety and depression.[18]

Interestingly, the GI tract and, more specifically, EECs are impacted by the gut microbiota, whose diversity and composition greatly influence a variety of gut hormones and peptides, such as ghrelin, peptide YY, glucagon-like peptide 1 (GLP-1), cholecystokinin (CCK), and neurotensin, hereafter discussed in more detail.[19]

Ghrelin: the hunger hormone. One of the key hormones involved in appetite regulation is ghrelin, often called the "hunger hormone." Ghrelin is primarily synthesized and secreted by the stomach when it is empty, signaling hunger and stimulating appetite. Ghrelin concentration rises before meals and decreases after food intake, reflecting the body's energy status and regulating meal initiation. The current scientific understanding is that ghrelin could be a key signaling molecule governing the communication between the GI tract and the CNS.[18]

Peptide YY and GLP-1: satiety signaling. Peptide YY and GLP-1 are gut-derived peptides that signal meal-ending satiation and inhibit appetite. EECs release peptide YY and GLP-1 in the distal small intestine and colon in response to nutrient intake; particularly to fat and protein in the case of peptide YY. GLP-1 secretion from EECs stimulates insulin secretion and suppresses

glucagon release to regulate blood glucose concentration.[18] GLP-1 receptor agonists have been at the forefront of recent research and medical intervention, having shown promise for weight management and glycemic control in individuals with obesity and patients with type 2 diabetes.

CCK: meal-related signaling. CCK is a gut peptide secreted by EECs in the duodenum and jejunum in response to nutrients—particularly fat and protein. CCK stimulates pancreatic enzyme secretion and gallbladder contraction, produces meal-ending satiation, inhibits gastric emptying, and modulates intestinal motility.[20] CCK receptors are expressed in the brain, where they modulate appetite and food intake. CCK concentration correlates positively with increased anxiety-like behaviors in both humans and mice, and CCK modulates mood disorders through other neurotransmitters, including glutamate, dopamine, acetylcholine, and GABA, all of which play important roles in emotional behaviors.[18]

Neurotensin: role in stress response. Neurotensin is a neuropeptide produced by EECs in the small intestine and colon in response to luminal nutrients and stress. Neurotensin stimulates the growth of intestinal mucosa under basal conditions and during periods of nutrient deprivation,[21] inhibits gastric acid secretion and motility, stimulates pancreatic and intestinal secretions, decreases adipose tissue blood flow, and increases small intestinal blood flow.[22] Dysregulation of neurotensin signaling has been implicated in the pathophysiology of several CNS disorders, such as schizophrenia, drug abuse, Parkinson disease, eating disorders, and cancer, as well as in CNS functions such as inflammation, pain, and central control of blood pressure.[23]

Dysregulation of hormone signaling and gut peptides. Dysregulation of hormone signaling and gut peptides in the gut-brain axis has been implicated in the pathogenesis of various GI and metabolic disorders, including obesity, diabetes, and eating disorders. Consequently, targeting gut hormones and peptides represents a promising approach for developing novel therapeutic interventions aimed at improving GI function, restoring metabolic homeostasis, supporting brain and cognitive function, and promoting health.

The role of gut microbes: exploring the microbiota-gut-brain axis

A revolution in medical research and health care is the growing understanding and awareness of how gut microbes influence systems outside of their immediate influence on the GI tract, including brain function and behavior. This blossoming field of study highlights the intricate relationship between the gut microbiota and the CNS.

The gut microbiota comprises trillions of microorganisms, including bacteria, viruses, fungi, parasites, and archaea, that inhabit the GI tract. Known collectively as the microbiome, these microorganisms have coevolved as integral to human physiology. Various factors, including diet, genetics, environment, and lifestyle, influence the composition of the gut microbiota.

Bacteria are the predominant members of the gut microbiota, with hundreds of different species present in the human gut. The dominant gut microbial phyla are Bacillota (formerly Firmicutes), Bacteroidota (formerly Bacteroidetes), Actinomycetota (formerly Actinobacteria), Pseudomonadota (formerly Proteobacteria),[24] Fusobacteriota, and Verrucomicrobiota, with Bacillota and Bacteroidota representing 90% of gut microbiota.[25]

Beyond taxonomic composition, the functional potential of the gut microbiota is shaped by the metabolic activities and gene expression profiles of its constituent microorganisms. The gut microbiome encodes over 3 million genes, producing thousands of metabolites, whereas the human genome consists of approximately 20 000 protein-coding genes.[26] This vast array of metabolites can be broadly divided into 3 types: (1) metabolites produced by gut microbiota directly from nutrient intake, such as short-chain fatty acids (SCFAs) and indole derivatives; (2) metabolites generated by the host and modified by gut microbiota, such as secondary bile acids; and (3) metabolites produced de novo, such as polysaccharide A. All these metabolites can influence host physiology, including gut and brain function.[27]

Gut microbes produce and metabolize hormones and neuropeptides, such as ghrelin and leptin, which regulate appetite, metabolism, and mood.[28] Microbial metabolites, such as SCFAs and bile acids, can also act as signaling molecules that modulate hormone secretion and energy homeostasis. SCFAs are generated by the fermentation by the gut microbiota of nonhost-digestible dietary fibers, with more than 95% of SCFAs derived from gut microbes being made up of acetate, propionate, and butyrate.[29] SCFAs are perhaps the most extensively studied molecules related to the influence of gut microbiota on host energy metabolism and appetite. However, they are also involved in immunomodulation and the regulation of regulatory T cells and exert crucial physiological effects on several organs, including the brain.[30]

Dysbiosis, or an imbalance in gut microbial composition, can lead to immune dysregulation and neuroinflammation, contributing to the pathogenesis of neurological and psychiatric disorders. Emerging evidence suggests that alterations in the gut microbiota may contribute to the development and progression of neurological disorders, such as Alzheimer disease, Parkinson disease, and multiple sclerosis. Furthermore, the gut microbiota has been implicated in the pathophysiology of psychiatric disorders, including depression, anxiety, and autism spectrum disorder. In addition to its effects on the brain, dysbiosis of the gut microbiota is associated with various GI conditions, such as IBD, IBS, and gastroesophageal reflux disease.

Therapeutic potential: harnessing the power of the microbiota

Microbiota-based therapies include dietary interventions, probiotics, prebiotics, antibiotics, phage therapy, fecal microbiota transplant, live biotherapeutics, and microbiome

mimetics. Each aims to modify the microbiota to treat disease and improve overall health.[31]

Probiotics are live microorganisms that confer health benefits when consumed in adequate amounts, while prebiotics are dietary fibers that selectively stimulate the growth of beneficial bacteria in the gut. Both probiotics and prebiotics modulate the composition and function of the gut microbiota and may have beneficial effects on mood and cognition, as well as GI function.

Diet plays a crucial role in shaping the gut microbiota, with certain foods promoting the growth of beneficial bacteria and others contributing to dysbiosis. The Mediterranean diet, rich in fruits, vegetables, whole grains, and fermented foods, has been associated with a more diverse and resilient gut microbiota and may confer protective effects against neurological and psychiatric disorders.[32] Advances in microbiome science have led to the development of novel microbial-based therapeutics, such as next-generation probiotics, synbiotics (prebiotics and probiotics in combination), and microbial-derived metabolites, or postbiotics. These interventions hold promise for modulating gut microbial composition and activity to improve GI function and, by extension, brain health—mitigating the risk of neurological and psychiatric disorders.

CONCLUSION

In summary, the gut microbiota, composed of trillions of microorganisms residing in the GI tract, plays a profound role in influencing host physiology. Dysbiosis, or imbalance in gut microbial composition, can lead to immune dysregulation, neuroinflammation, and the development of neurological and psychiatric disorders.

Overall, a deeper understanding of the gut-brain connection and the role of the gut microbiota in modulating brain function opens up new avenues for therapeutic interventions, such as dietary interventions, aimed at improving both GI health and mental well-being. By harnessing the power of the microbiota-gut-brain axis, we may be able to develop novel strategies for preventing and treating a wide range of neurological and psychiatric disorders, ultimately improving overall health and quality of life.

REFERENCES

1. Radford-Smith DE, Anthony DC. Prebiotic and Probiotic Modulation of the Microbiota-Gut-Brain Axis in Depression. *Nutrients*. 2023;15(8):1880. Published 2023 Apr 13. doi:10.3390/nu15081880
2. Murthy PM, Ca J, Kandi V, et al. Connecting the Dots: The Interplay Between Stroke and the Gut-Brain Axis. *Cureus*. 2023;15(4):e37324. Published 2023 Apr 9. doi:10.7759/cureus.37324
3. Kennedy PJ, Cryan JF, Dinan TG, Clarke G. Irritable bowel syndrome: a microbiome-gut-brain axis disorder?. *World J Gastroenterol*. 2014;20(39):14105-14125. doi:10.3748/wjg.v20.i39.14105
4. Richard Câmara, Christoph J. Griessenauer. Chapter 27: Anatomy of the Vagus Nerve. Academic Press, 2015; Pages 385-397. ISBN 9780124103900. doi.org/10.1016/B978-0-12-410390-0.00028-7
5. Han Y, Wang B, Gao H, et al. Vagus Nerve and Underlying Impact on the Gut Microbiota-Brain Axis in Behavior and Neurodegenerative Diseases. *J Inflamm Res*. 2022;15:6213-6230. Published 2022 Nov 9. doi:10.2147/JIR.S384949
6. Williams EK, Chang RB, Strochlic DE, Umans BD, Lowell BB, Liberles SD. Sensory Neurons that Detect Stretch and Nutrients in the Digestive System. *Cell*. 2016;166(1):209-221. doi:10.1016/j.cell.2016.05.011
7. Holland AM, Bon-Frauches AC, Keszthelyi D, Melotte V, Boesmans W. The enteric nervous system in gastrointestinal disease etiology. *Cell Mol Life Sci*. 2021;78(10):4713-4733. doi:10.1007/s00018-021-03812-y
8. Fung C, Vanden Berghe P. Functional circuits and signal processing in the enteric nervous system. *Cell Mol Life Sci*. 2020;77(22):4505-4522. doi:10.1007/s00018-020-03543-6
9. Mittal R, Debs LH, Patel AP, et al. Neurotransmitters: The Critical Modulators Regulating Gut-Brain Axis. *J Cell Physiol*. 2017;232(9):2359-2372. doi:10.1002/jcp.25518
10. Chen Y, Xu J, Chen Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients*. 2021;13(6):2099. Published 2021 Jun 19. doi:10.3390/nu13062099
11. Margoob MA, Kouser S, Jan N. Serotonin: The Link between Gut Microbiome and Brain. In: *IntechOpen eBooks*. ; 2024. doi:10.5772/intechopen.1003826
12. Chen Y, Xu J, Chen Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients*. 2021;13(6):2099. Published 2021 Jun 19. doi:10.3390/nu13062099
13. Tsai LH. Function of GABAergic and glutamatergic neurons in the stomach. *J Biomed Sci*. 2005;12(2):255-266. doi:10.1007/s11373-005-1357-0
14. Chavan SS, Pavlov VA, Tracey KJ. Mechanisms and Therapeutic Relevance of Neuro-immune Communication. *Immunity*. 2017;46(6):927-942. doi:10.1016/j.immuni.2017.06.008
15. Peppas S, Pansieri C, Piovani D, et al. The Brain-Gut Axis: Psychological Functioning and Inflammatory Bowel Diseases. *J Clin Med*. 2021;10(3):377. Published 2021 Jan 20. doi:10.3390/jcm10030377
16. Ge L, Liu S, Li S, et al. Psychological stress in inflammatory bowel disease: Psychoneuroimmunological insights into bidirectional gut-brain communications. *Front Immunol*. 2022;13:1016578. Published 2022 Oct 6. doi:10.3389/fimmu.2022.1016578
17. Chen Y, Xu J, Chen Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients*. 2021;13(6):2099. Published 2021 Jun 19. doi:10.3390/nu13062099
18. Sun LJ, Li JN, Nie YZ. Gut hormones in microbiota-gut-brain cross-talk. *Chin Med J (Engl)*. 2020;133(7):826-833. doi:10.1097/CM9.0000000000000706
19. Roh E, Choi KM. Hormonal Gut-Brain Signaling for the Treatment of Obesity. *Int J Mol Sci*. 2023;24(4):3384. Published 2023 Feb 8. doi:10.3390/ijms24043384
20. Geary N. Cholecystokinin (CCK). In: *Elsevier eBooks*. ; 2018:529-533. doi:10.1016/b978-0-12-801238-3.95866-5
21. Rock SA, Jiang K, Wu Y, et al. Neurotensin Regulates Proliferation and Stem Cell Function in the Small Intestine in a Nutrient-Dependent Manner. *Cell Mol Gastroenterol Hepatol*. 2022;13(2):501-516. doi:10.1016/j.jcmgh.2021.09.006
22. Shulkes A. Neurotensin. In: *Elsevier eBooks*. ; 2004:346-349. doi:10.1016/b0-12-475570-4/00917-3
23. Boules M, Li Z, Smith K, Fredrickson P, Richelson E. Diverse roles of neurotensin agonists in the central nervous system. *Front Endocrinol (Lausanne)*. 2013;4:36. Published 2013 Mar 22. doi:10.3389/fendo.2013.00036
24. Genome Web. Bacillota AKA Firmicutes. January 6, 2022. Accessed March 11, 2024. https://www.genomeweb.com/scan/bacillota-aka-firmicutes
25. Rinninella E, Raoul P, Cintoni M, et al. What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. *Microorganisms*. 2019;7(1):14. Published 2019 Jan 10. doi:10.3390/microorganisms7010014
26. Amaral P, Carbonell-Sala S, De La Vega FM, et al. The status of the human gene catalogue. Nature. 2023;622(7981):41-47. doi:10.1038/s41586-023-06490-x
27. Liu J, Tan Y, Cheng H, Zhang D, Feng W, Peng C. Functions of Gut Microbiota Metabolites, Current Status and Future Perspectives. *Aging Dis*. 2022;13(4):1106-1126. Published 2022 Jul 11. doi:10.14336/AD.2022.0104
28. Clemente-Suárez VJ, Redondo-Flórez L, Rubio-Zarapuz A, Martín-Rodríguez A, Tornero-Aguilera JF. Microbiota Implications in Endocrine-Related Diseases: From Development to Novel Therapeutic Approaches. *Biomedicines*. 2024; 12(1):221. https://doi.org/10.3390/biomedicines12010221
29. Van De Wouw, M., Schellekens, H., Dinan, T. G., & Cryan, J. F. (2017). Microbiota-Gut-Brain axis: modulator of host metabolism and appetite. *The Journal of Nutrition*, *147*(5), 727–745. https://doi.org/10.3945/jn.116.240481
30. Silva, Y. P., Bernardi, A., & Frozza, R. L. (2020). The role of Short-Chain fatty acids from gut microbiota in Gut-Brain communication. *Frontiers in Endocrinology*, *11*. https://doi.org/10.3389/fendo.2020.00025
31. Gulliver EL, Young RB, Chonwerawong M, et al. Review article: the future of microbiome-based therapeutics. *Aliment Pharmacol Ther*. 2022;56(2):192-208. doi:10.1111/apt.17049
32. Barber TM, Kabisch S, Pfeiffer AFH, Weickert MO. The Effects of the Mediterranean Diet on Health and Gut Microbiota. *Nutrients*. 2023;15(9):2150. Published 2023 Apr 29. doi:10.3390/nu15092150