Molecular Links Between Gut Serotonin and Enteric Neural Signaling

Introduction

Gut–brain communication has emerged as a central topic in neuroscience and medicine, linking digestion, emotion, and neurochemical regulation. At the heart of this connection is serotonin, a neurotransmitter that regulates mood, sleep, and gut motility. Interestingly, approximately 95% of the body's serotonin is produced in the gastrointestinal tract rather than the brain. Understanding how gut-derived serotonin interacts with the enteric nervous system (ENS)—the intrinsic neural network of the digestive tract—is key to decoding the molecular foundations of the brain–gut signaling. This review aims to explore the specific molecular pathways that mediate serotonin's role in the ENS, drawing on four major studies that examine its synthesis, receptor mechanisms, and microbiota-driven regulation. By comparing recent findings, this review identifies shared mechanisms, divergent results, and the ongoing gaps in serotonin–ENS research.

Summary of the Papers

Del Colle et al. (2019) reviewed the fundamental role of serotonin in bidirectional gut–brain signaling, emphasizing that nearly all serotonin in the body is synthesized by enterochromaffin (EC) cells. Using molecular mapping and neural tracing, this study showed that serotonin modulates gastrointestinal motility, secretion, immune function, and pain perception. Importantly, serotonin activates 5‑HT receptors on both enteric and vagal neurons, establishing a communication loop between the gut and central nervous system. The paper also highlighted

how dysregulated serotonergic signaling contributes to conditions such as irritable bowel syndrome (IBS), anxiety, and depression.

Mawe, Hoffman, and Gershon (2013) conducted a mechanistic study of serotonin signaling in the gastrointestinal tract. Their findings clarified that EC cells synthesize serotonin via tryptophan hydroxylase 1 (TPH1) and release it into the lamina propria in response to chemical or mechanical stimuli. Once released, serotonin binds to specific 5-HT receptor subtypes—such as 5-HT3 and 5-HT4—on nearby enteric neurons, influencing peristalsis, secretion, and pain transmission. The serotonin-selective reuptake transporter (SERT) terminates the signal by clearing serotonin from the synapse, maintaining precise regulation. Disruptions in this system can result in visceral hypersensitivity or abnormal gut motility.

De Vadder et al. (2018) expanded this understanding by demonstrating the influence of the gut microbiota on serotonin signaling and ENS development. Through controlled experiments in germ-free mice, the study revealed that microbial populations stimulate EC cell serotonin production, which acts through $5\text{-}HT_4$ receptors to promote ENS neuron survival and maturation. Restoration of microbiota or serotonin precursors in germ-free models reinstated normal ENS development, proving that gut microbes play a vital regulatory role.

Kim and Camilleri (2000) provided an integrative review linking gut-derived serotonin with both gastrointestinal and central nervous system function. Their work synthesized clinical and molecular data to explain how serotonin mediates the brain–gut connection. They identified serotonin receptor modulation as a therapeutic target for disorders such as IBS and depression, highlighting the translational potential of molecular discoveries.

Compare and Analyze Themes

Theme 1: Serotonin as a Gut-Derived Neural Mediator

Across studies, serotonin consistently emerges as the key molecule facilitating gut–neural communication. Both Del Colle et al. (2019) and Mawe et al. (2013) describe serotonin's local production by EC cells and its receptor-specific signaling to ENS neurons. The overlap in their findings reinforces serotonin's role as both a neurotransmitter and paracrine signaling molecule. Gershon emphasizes the functional outcomes—motility and immune regulation—whereas Mawe et al. dissect the cellular mechanisms, including synthesis and reuptake. Together, these studies establish the foundational biochemical framework of serotonin signaling in the ENS.

Theme 2: Microbiota and ENS Plasticity

De Vadder et al. (2018) introduced a new dimension by showing that microbial ecosystems regulate serotonin production and ENS development. Their findings suggest that serotonin not only mediates communication but also guides neuronal growth and plasticity. This discovery bridges gastroenterology and microbiology, revealing how microbial health directly shapes neural function. In contrast, earlier studies (Mawe et al., 2013) focused on molecular mechanisms independent of microbial influence, indicating that serotonin's regulatory context has broadened over time.

Theme 3: Clinical and Translational Implications

Kim and Camilleri (2000) extend these mechanistic insights to human health, linking serotonin dysregulation to both gastrointestinal and psychiatric disorders. They highlight that therapeutic strategies targeting serotonin receptors could alleviate symptoms across systems, supporting serotonin's systemic influence. This translational perspective complements the molecular focus of Del Colle et al. (2019) and De Vadder et al. (2018), forming a cohesive picture of serotonin as a molecular hub connecting gut, brain, and microbiota interactions.

Limitations and Gaps

Despite growing evidence, several limitations remain. Many of the foundational studies rely on animal or in vitro models, limiting direct translation to human systems. Sample sizes in microbiota–ENS research are often small, and interspecies variability complicates cross-comparison. Moreover, most studies focus on short-term outcomes, leaving longitudinal effects of serotonin modulation underexplored. Few have investigated population-level differences or diet-related serotonin variations, representing an important gap in understanding how environmental factors shape ENS signaling.

Conclusion and Future Directions

Together, these studies reveal serotonin as a critical molecular link between the gut and the enteric nervous system. Produced primarily by EC cells and regulated by microbial activity, serotonin activates distinct receptor pathways to coordinate motility, secretion, and pain processing. This network underscores the complexity of gut–brain communication and the potential for cross-disciplinary research integrating neuroscience, microbiology, and clinical medicine. Future studies should examine how diet, antibiotics, and probiotics influence serotonin signaling, and how receptor-specific therapies could improve gastrointestinal and mental health outcomes. Advancing this research will be vital for developing new treatments for disorders rooted in serotonin imbalance.

References

De Vadder, F., Grasset, E., Manneras Holm, L., et al. (2018). *Gut microbiota regulates maturation of the adult enteric nervous system via enteric serotonin networks.*

Proceedings of the National Academy of Sciences of the United States of America, 115(25), 6458–6463. https://doi.org/10.1073/pnas.1720017115

Del Colle, A., et al. (2019). *Novel aspects of enteric serotonergic signalling in health and brain–gut communication. American Journal of Physiology – Gastrointestinal and Liver Physiology, 317*(3), G331–G346. https://doi.org/10.1152/ajpgi.00173.2019

Kim, D. Y., & Camilleri, M. (2000). *Serotonin: A mediator of the brain–gut connection. American Journal of Gastroenterology, 95*(10), 2698–2709. https://doi.org/10.1111/j.1572-0241.2000.03177.x

Mawe, G. M., Hoffman, J. M., & Gershon, M. D. (2013). *Serotonin-signalling in the gastrointestinal tract: Functions, dysfunctions and therapeutic targets. Nature Reviews Gastroenterology & Hepatology, 10*(8), 473–486. https://doi.org/10.1038/nrgastro.2013.105