

The interplay of gut microbiota and intestinal motility in gastrointestinal function

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Abstract

The relationship between gut microbiota and intestinal motility is crucial for maintaining gastrointestinal health. Intestinal motility refers to the coordinated movements of the digestive tract, essential for effective digestion, nutrient absorption, and timely waste elimination. Recent studies have demonstrated that microbiota play a crucial role not only in the maturation of intestinal motility but also in the ongoing maintenance of established motility patterns. Disruptions in motility can lead to various disorders, such as chronic constipation, irritable bowel syndrome, and chronic idiopathic pseudo-obstruction. Gut microbiota significantly influence intestinal motility through mechanisms like bile acid metabolism and the production of short-chain fatty acids. In patients with diarrhea-predominant irritable bowel syndrome, elevated primary-to-secondary bile acid ratios suggest a complex interaction between gut bacteria and bile acids that can enhance motility via receptors like TGR5. Additionally, the role of interstitial cells of Cajal in facilitating non-neuronal contractions has revolutionized our understanding of motility regulation, highlighting both neural and non-neuronal factors. Various therapeutic approaches, including prebiotics, probiotics, and fecal microbiota transplantation, have been explored to improve intestinal motility, although their effectiveness has been limited. Advancements in gene-related research and innovative diagnostic methods are vital for a deeper understanding of how the gut microbiome regulates motility. This review synthesizes current knowledge on the interplay between gut microbiota and intestinal motility, emphasizing the need for interdisciplinary research to develop effective treatments targeting gut microbiota for gastrointestinal disorders. By unraveling these complex interactions, we can pave the way for novel therapeutic strategies that enhance intestinal health and improve the quality of life for those affected by motility-related disorders.

Key words: gut microbiota, intestinal motility, smooth muscle, enteric nervous system, muscularis macrophages

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Introduction

The intricate relationship between intestinal motility and gut microbiota has garnered increasing attention in recent years, emphasizing their critical roles in maintaining human health (1–3). Intestinal motility, the coordinated movement of the digestive tract, is essential for the proper digestion and absorption of nutrients and the timely excretion of waste. An imbalance in this motility can lead to various gastrointestinal disorders, including chronic constipation (4), irritable bowel syndrome (IBS) (5), and chronic idiopathic pseudo-obstruction (CIPO) (6), all of which are characterized by altered intestinal movement.

Emerging research has revealed that the gut microbiota, a diverse community of microorganisms residing in the intestine, plays a pivotal role in regulating systemic homeostasis. Recent studies have shown that microbiota is not only essential for the maturation of intestinal motility but also crucial for maintaining optimal motility throughout life (7). Beyond aiding in absorbing essential nutrients such as carbohydrates, lipids, and vitamins, gut bacteria produce metabolites like short-chain fatty acids (SCFAs) and bile acids, which significantly influence host physiology (8). SCFAs, generated through the fermentation of dietary fibers by gut bacteria such as *Lactobacillus* and *Bifidobacterium*, contribute to energy provision for colon cells, metabolic regulation, and immune modulation (9). Likewise, bile acids, which are modified by gut microbes *Clostridium* species, are critical for lipid metabolism and signal transduction (10).

Importantly, the relationship between gut microbiota and intestinal motility is bidirectional; while motility affects the composition and distribution of gut bacteria, the microbiota also exerts a regulatory influence on motility itself (11). This dynamic interplay raises crucial questions regarding the mechanisms behind gut bacteria's effects on the enteric nervous system and intestinal smooth muscle—the two primary components governing intestinal contractions (12, 13).

Given the link between dysbiosis, or alterations in gut microbial composition, and motility disorders, understanding this complex interaction is paramount for developing novel therapeutic strategies. Targeting the gut microbiota offers a promising avenue for intervention in gastrointestinal diseases characterized by motility dysfunction. This review aims to elucidate the mechanisms by which gut bacteria influence intestinal motility, highlighting their implications for both health and disease and paving the way for innovative treatment approaches.

The Role of Gut Microbiota in the Development and Regulation of the Enteric Nervous System

The interplay between gut microbiota and the enteric nervous system (ENS) is fundamental to the regulation of gastrointestinal motility. During fetal development, intestinal motility is minimal, particularly in the large intestine, as gut microbiota is not yet present. Postnatally, the introduction of external bacteria plays a critical role in establishing the gut microbiota, which subsequently enhances gastrointestinal activity and motility.

Research utilizing germ-free mice models has provided significant insights into this relationship. Studies conducted by Collins et al. revealed that neonatal germ-free mice exhibit substantially reduced intestinal motility compared to specific-pathogen-free (SPF) mice. This diminished motility is associated with a notable decrease in neuronal density within the myenteric plexus, which governs gut movement, particularly in the jejunum and ileum. Interestingly, while the total number of ganglion neurons was lower, the proportion of neurons producing nitric oxide (NO) was found to be higher in germ-free conditions. Given that NO acts as a signaling

molecule facilitating relaxation in intestinal smooth muscles, this increased proportion of NO-producing neurons suggests a mechanistic link to the observed reduction in muscle contraction and overall motility.

The significance of gut microbiota goes beyond neonatal development; it also plays a crucial role in maintaining the ENS in adult mice. Research has shown that adult germ-free mice exhibit decreased neuronal density in the colonic region and reduced intestinal motility compared to their SPF counterparts. Notably, when fecal material from SPF mice was transplanted into germ-free mice, it resulted in an increase in serotonin (5-HT) production within both the intestinal mucosa and the neuronal populations. This elevated 5-HT level is essential for promoting neuronal growth and enhancing gut motility, thereby partially restoring normal intestinal function. Additionally, SCFAs produced by microbiota stimulate 5-HT production in enterochromaffin cells, further influencing motility. These findings highlight the critical role of gut microbiota in both the development and ongoing maintenance of the ENS, which is vital for normal gastrointestinal motility.

Recent studies highlight the aryl hydrocarbon receptor (AHR) as a crucial player in the relationship between gut microbiota and the ENS. AHR acts as a biosensor, detecting changes in gut microbial conditions and regulating colonic motility (14). Additionally, gut microbiota influences the structure and function of the jejunal ENS by modulating myenteric vasoactive intestinal peptide (VIP), which regulates cholinergic nerves. This process relies on crosstalk between the microbiota and the innate immune system, particularly involving MYD88/TRIF pathways and enteric glial cells. The presence and stability of microbiota are vital for maintaining normal myenteric VIP levels and intestinal motility. Notably, altered jejunal VIP levels in patients with severe constipation underscore the clinical relevance of these findings (7).

Gut Microbiota and Intestinal Smooth Muscle

Isolated live intestinal tissue specimens exhibit peristaltic movement under *ex vivo* conditions; however, this response is inhibited when nerve activity is blocked using tetrodotoxin. Traditionally, this observation led to the belief that the neural network connecting the layers of muscle is essential for intestinal motility. However, subsequent research has shown that intestinal smooth muscle strips can still generate spontaneous contractions even in the absence of neural input. Huizinga et al. identified that interstitial cells of Cajal (ICC), located within the myenteric plexus and muscularis propria, are responsible for these non-neuronal contractions (15, 16). Additionally, Kaji and Hori have enhanced our understanding of the close relationship between networks of interstitial cells of Cajal and gastrointestinal transit *in vivo* (17).

Resident macrophages, known as Muscularis Macrophages (MM ϕ), are strategically located near ICC in the muscularis propria. These macrophages play a crucial role in immune responses and also affect intestinal motility. Mikkelsen et al. were the first to suggest that MM ϕ could induce inflammation in the muscularis propria, potentially leading to dysfunction in intestinal motility (18). Following this, Eskandari et al. demonstrated in a model of intestinal motility dysfunction related to lipopolysaccharides (LPS)-induced sepsis that LPS stimulates the production of NO in MM ϕ , which in turn reduces intestinal motility (19). Furthermore, research using a postoperative ileus model indicated a strong correlation between the activation of MM ϕ and damage to ICC (20). The intestinal mucosal epithelium serves primarily as a barrier, characterized by tight junctions and a mucin layer. However, recent findings suggest that gut microbiota can affect the activity of muscle macrophages (MM ϕ) in the muscle layer. A reduction in MM ϕ has been linked to intestinal motility dysfunction seen in antibiotic-treated specific pathogen-free (SPF) mice. Conversely, an increase in MM ϕ numbers has been associated with improved motility in germ-free mice administered LPS (21). Furthermore, recent studies have indicated that fecal transplants from either young or aged mice to germ-free mice resulted

in decreased intestinal motility for those receiving transplants from aged mice. This reduction is believed to be caused by inflammation triggered by the activation of MM ϕ (22). The role of MM ϕ in intestinal motility varies depending on context. Under inflammatory conditions, MM ϕ inhibits motility through the production of nitric oxide. Conversely, in a normal physiological state, MM ϕ facilitates homeostatic motility.

This body of evidence emphasizes that gut microbiota play a role in regulating intestinal motility by interacting with ICC through MM ϕ . Despite the recognized influence of MM ϕ numbers and immune activity on intestinal motility, the specific mechanisms involved remain to be fully understood.

Gut Microbiota and Intestinal Motility: Mechanisms of Action

Studies have shown a causal role for gut motility in shaping microbiota composition, independent of diet or host genetics. Studies demonstrate that slowed transit alters luminal pH, nutrient availability, and clearance rates, thereby creating a selective environment that favors specific microbial taxa, such as methanogens, while reducing overall diversity. This directional influence has been confirmed in both human cohorts and in vitro models, where motility changes led to reproducible shifts in microbial community structure and metabolic profiles (2, 23–25). These findings underscore the importance of incorporating motility parameters into microbiome research and suggest that therapeutic modulation of transit time could be a viable strategy to restore microbial balance in gut dysbiosis.

Recent research has clarified how gut microbiota regulates intestinal motility through various mechanisms involving the host's intestinal immune system, endocrine system, and gut microbial metabolites. A significant aspect of this process is the role of Toll-like receptors (TLRs), which identify pathogen-associated molecular patterns derived from microbes during the immune response of the human host to gut microorganisms.

Initially, TLRs were thought to be present only in immune cells (26). However, it has since been discovered that they are also found in nerve cells. Research has shown that TLR4 knockout mice raised in SPF conditions, as well as wild-type mice in germ-free environments, exhibit significantly reduced intestinal motility compared to their wild-type counterparts in SPF conditions. When enteric neuronal cells are incubated with LPS, there is an activation of the transcription factor nuclear factor (NF)- κ B, leading to increased cell survival. The interactions between enteric neurons and microbes enhance neuron survival and gastrointestinal motility in mice. The activation of TLR4 and NF- κ B by LPS seems to promote the survival of enteric neurons. Understanding the factors that regulate TLR4 signaling in neurons could lead to methods for modifying gastrointestinal motility (27). Additionally, another study demonstrated that administering TLR2 receptor agonists or antagonists to wild-type mice under SPF conditions either enhanced or decreased intestinal motility, respectively. Furthermore, the administration of antibiotics resulted in reduced TLR2 expression in intestinal nerves and a decline in intestinal motility. This finding underscores the importance of TLR2 activation by gut bacteria in the development of intestinal nerves and the maintenance of normal intestinal motility function (28).

In patients with IBS, studies have shown that gastrointestinal hormones involved in intestinal motility, such as 5-HT, GLP-1, GIP, cholecystokinin, ghrelin, and motilin, are altered compared to control groups. Research has also highlighted the relationship between these gastrointestinal hormones and gut microbiota. Among these hormones, 5-HT stands out as particularly significant (29). 5-HT functions both as a gastrointestinal hormone and as a neurotransmitter. It is primarily located in the gastrointestinal tract (90%), followed by platelets (8%) and the central nervous system (2%), making the gastrointestinal tract the largest source of 5-HT production. 5-HT is synthesized from the essential amino acid tryptophan through the intermediate 5-hydroxytryptophan in enteroendocrine cells, specifically in cells known as enterochromaffin and entero-

chromaffin-like cells. It plays a central role in regulating intestinal motility. Research indicates that the production of 5-HT is significantly reduced in germ-free mice and mice treated with antibiotics (30, 31). This suggests that gut microbiota may play a role in 5-HT production. However, it has become clear that this relationship is mediated by gut microbial metabolites.

Key gut microbial metabolites that play a significant role in intestinal motility are short-chain fatty acids (SCFAs) and secondary bile acids. When gut bacteria ferment dietary fiber (non-digestible saccharides) in the colon, they produce SCFAs such as acetate, propionate, and butyrate. These SCFAs primarily act on enteroendocrine cells in the intestinal epithelium, leading to an indirect promotion of intestinal motility through the production of 5-HT (32). Additionally, SCFAs may also enhance intestinal motility directly by stimulating intestinal smooth muscle and inducing contraction responses that are resistant to tetrodotoxin and dependent on calcium (33).

In contrast, primary bile acids like cholic acid and chenodeoxycholic acid are synthesized in the liver, where they conjugate with glycine or taurine before being secreted into the intestinal tract. Within the gut, these primary bile acids can be deconjugated and transformed into secondary bile acids, such as deoxycholic and lithocholic acids, through the action of gut bacteria. This conversion highlights the essential role of gut microbiota in regulating both the total bile acid content and the ratio of primary to secondary bile acids in the intestines.

Recent studies involving patients with diarrhea-predominant irritable bowel syndrome (IBS-D) have demonstrated that, even with unchanged total bile acid levels in stool samples, there is often an elevated primary/secondary bile acid ratio. This finding suggests a significant influence of gut bacteria on intestinal motility mediated by bile acid metabolism (34, 35). Furthermore, basic research using animal models, such as rabbits and guinea pigs, supports the idea that bile acids can effectively promote intestinal motility (36, 37). One proposed mechanism for this effect is the enhancement of 5-HT production via the bile acid receptor known as Transmembrane G-protein coupled receptor (TGR5) found on enteroendocrine cells (38). An important clinical application of this knowledge is the use of Elobixibat, a drug that inhibits the ileal bile acid transporter (IBAT) in intestinal epithelial cells. By reducing bile acid reabsorption in the terminal ileum, Elobixibat increases the concentration of bile acids in the large intestine, thereby enhancing intestinal motility. Its recent adoption as a therapeutic agent for chronic constipation has reinforced the understanding of the relationship between gut bacteria-derived bile acids and intestinal motility.

Conclusion

Precise control of intestinal motility is crucial for maintaining human life and enhancing quality of life. Recent studies have shown that gut microbiota play a significant role in developing and maintaining intestinal motility (Fig. 1). Research in this area has progressed through various approaches, including basic studies using germ-free and genetically modified animal models and clinical research focused on the human gut microbiome.

Several treatments have been explored to improve intestinal motility, such as the administration of prebiotics and probiotics, antibiotic therapy, and even fecal microbiota transplantation. However, the effects of these therapies are still limited. Since the complete sequencing of the human genome was accomplished in 2003, there has been substantial advancement in gene-related research and treatment. In contrast, the complete understanding of the human gut microbiota as a metagenome remains incomplete, and treatments targeting the gut microbiota are still in development. Additionally, current diagnostic methods make evaluating human intestinal motility in real-time during clinical practice challenging, highlighting the urgent need for innovative diagnostic techniques. Fortunately, advancements in data analysis technology, wearable devices, and the

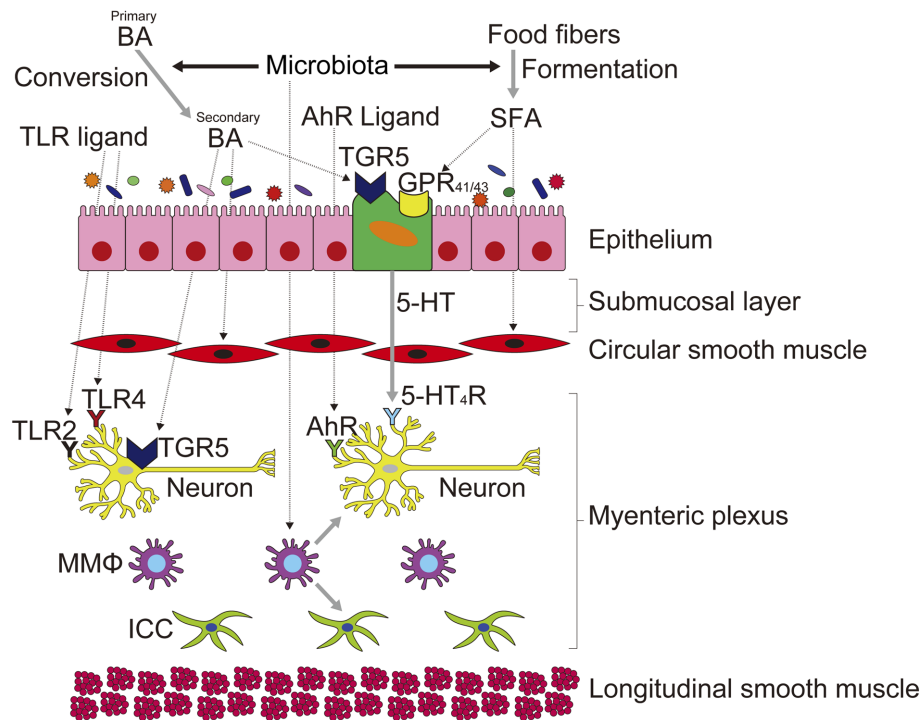


Fig. 1. The gut microbiota plays a critical role in modulating intestinal motility via a multifaceted network of signaling pathways. (A) Epithelial and Enteroendocrine Signaling: Dietary fiber is metabolized by gut microbiota into short-chain fatty acids (SCFAs), which activate G-protein coupled receptors (GPR41 and GPR43) on enteroendocrine cells within the epithelium, promoting the release of serotonin (5-HT). Additionally, primary bile acids (BA) undergo transformation by gut microbiota into secondary bile acids, which subsequently activate TGR5 receptors on enteroendocrine cells. These signaling mechanisms significantly impact neuronal activity and intestinal motility. (B) Neuronal Modulation: Components derived from microbes serve as ligands for Toll-like receptors (TLR2 and TLR4) located on enteric neurons, thereby modulating their function. Furthermore, microbial ligands can activate the aryl hydrocarbon receptor (AhR) found in both epithelial cells and enteric neurons, further influencing gut motility. (C) Interaction of Muscularis Macrophages and Interstitial Cells of Cajal: Muscularis macrophages (MMφ) within the muscularis propria engage with interstitial cells of Cajal (ICC), which are essential for regulating smooth muscle contractility and, consequently, intestinal motility. This figure summarizes the integrated mechanisms by which gut microbiota regulates motility in the gastrointestinal tract.

development of medical devices, such as implantable devices, have made significant strides in various medical fields. Therefore, by engaging in research that integrates these diverse interdisciplinary fields, we hope to effectively control intestinal motility by targeting gut microbiota in the near future.

Conflicts of Interest

None.

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