Gut Microbiota-derived Metabolites Regulate Intestinal Motility in Constipation: Mechanisms and Therapeutic Implications

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Abstract

Constipation is a common gastrointestinal disorder characterized by infrequent bowel movements, difficult stool passage, excessive straining, and impaired colonic transit. Increasing evidence indicates that gut microbiota-derived metabolites are active regulators of intestinal motility rather than passive byproducts of luminal fermentation. In constipation, dysbiosis is often accompanied by reduced saccharolytic fermentation, altered bile acid biotransformation, disturbed tryptophan metabolism, and enhanced methanogenesis, all of which may contribute to delayed transit and stool desiccation. Short-chain fatty acids, secondary bile acids, tryptophan-derived metabolites, and methane influence motility through effects on enterochromaffin cells, serotonin biosynthesis, epithelial secretion, enteric neural circuits, mucosal immunity, and smooth muscle activity. These mechanistic insights have therapeutic implications. Dietary modulation, probiotics, synbiotics, fecal microbiota transplantation, and bile acid-targeted therapies may improve constipation partly by restoring a more favorable metabolite milieu. However, the causal role of individual metabolites in human constipation remains incompletely defined, and clinical responses are heterogeneous. This review summarizes current evidence on how gut microbiota-derived metabolites regulate intestinal motility in constipation and discusses the translational potential of metabolite-informed therapeutic strategies.

Keywords

Constipation, Gut microbiota, Microbial metabolites, Intestinal motility, Short-chain fatty acids, Bile acids, Tryptophan metabolism, Methane

Introduction

Chronic constipation is a highly prevalent gastrointestinal disorder that substantially impairs quality of life and imposes a considerable healthcare burden [1]. Contemporary guidelines emphasize that constipation is a heterogeneous condition involving altered transit, impaired secretion, anorectal dysfunction, and disturbed gut-brain communication rather than a simple reduction in bowel frequency [2]. This heterogeneity partly explains the marked interindividual variability in symptoms and treatment response.

Over the past decade, gut microbiota has emerged as an important component of constipation pathophysiology [3]. Early studies mainly described taxonomic alterations in constipated patients, whereas more recent work has highlighted microbial function and metabolic output as more informative mechanistic indicators [4]. The intestinal microbiota acts as a biochemical organ that ferments dietary substrates, modifies host-derived molecules, and generates bioactive compounds capable of influencing gastrointestinal motility, secretion,

mucosal immunity, and neuronal signaling [5].

Metabolomic studies increasingly support this concept. Compared with healthy individuals, patients with functional constipation often exhibit altered fecal and serum metabolic profiles, including reduced short-chain fatty acid (SCFA)-related signatures, disturbances in amino acid and tryptophan metabolism, altered bile acid composition, and shifts in pathways related to fermentation and gas production. These observations suggest that the functional consequences of dysbiosis may be mediated largely through changes in microbial metabolites. Accordingly, understanding how these metabolites regulate intestinal motility may help refine both mechanistic models and therapeutic strategies for constipation.

The gut microbiota-motility axis in constipation

The relationship between the gut microbiota and intestinal motility is bidirectional. Transit time shapes the intestinal ecosystem by altering nutrient exposure, oxygen gradients, luminal pH, and the time available for microbial fermentation. In turn, microbial metabolites regulate intestinal propulsion, secretion, epithelial integrity, and neuromuscular communication. Constipation may therefore both result from and further reinforce microbial dysfunction.

Experimental evidence indicates that intestinal microbes participate in the development and maintenance of normal motility patterns. Reigstad et al. demonstrated that gut microbes promote colonic serotonin production through effects on enterochromaffin cells, providing one of the clearest mechanistic links between microbial metabolism and host motility control [6]. In clinical settings, slower transit may favor methanogenesis and prolonged protein fermentation, whereas reduced intake of fermentable substrates may diminish saccharolytic activity and the generation of pro-motility metabolites. These interacting changes can create a self-perpetuating cycle in which dysbiosis and dysmotility aggravate one another.

Importantly, not all microbiota-associated changes in constipation are taxonomic. Functional shifts in microbial metabolism may be more directly relevant to motor physiology than compositional differences alone. This has shifted current research from descriptive dysbiosis toward metabolite-mediated host signaling.

Short-chain fatty acids and saccharolytic fermentation

Overview of SCFA biology

SCFAs, mainly acetate, propionate, and butyrate, are generated by microbial fermentation of dietary fiber and resistant starch. They are among the most abundant microbiota-derived metabolites in the colon and play major roles in epithelial energy supply, barrier maintenance, immune regulation, and luminal physiology [7]. Because of their abundance and broad biological activity, SCFAs have long been considered key mediators of microbiota-host communication.

SCFAs as regulators of motility

SCFAs influence intestinal motility through several complementary mechanisms. A classical human study demonstrated that intraluminal SCFAs stimulate ileal motility. Later mechanistic work linked these effects to free fatty acid receptors such as GPR41 and GPR43, supporting the view that SCFAs regulate intestinal movement through receptor-dependent epithelial and neural pathways.

One of the most important discoveries in this field was the demonstration that gut microbes enhance colonic serotonin biosynthesis through SCFA-dependent stimulation of enterochromaffin cells. Serotonin is a critical mediator of peristaltic reflexes and epithelial secretion. This finding provides a biologically plausible explanation for how impaired microbial fermentation may contribute to delayed transit in constipation.

SCFAs may also influence motility indirectly by modulating fluid and electrolyte handling, supporting colonocyte function, and maintaining mucosal integrity. Although their physiological effects may vary according to intestinal segment, luminal concentration, and receptor distribution, reduced saccharolytic fermentation is generally considered unfavorable for propulsive motility in constipation.

SCFAs in constipation

Metabolomic analyses in functional constipation frequently identify reduced SCFA-associated signatures or impaired carbohydrate fermentation capacity. These findings are consistent with the clinical observation that inadequate intake of fermentable substrates may worsen constipation and that selected dietary interventions can improve bowel habits in some patients [8]. However, the

response to dietary fiber remains heterogeneous, likely reflecting differences in microbiota composition, fermentation capacity, and constipation phenotype.

Bile acids and microbiota-dependent bile acid transformation

Microbial remodeling of the bile acid pool

Bile acids are synthesized in the liver and extensively modified by gut microbes through deconjugation and transformation into secondary bile acids [9]. These microbial conversions alter receptor affinity, physicochemical properties, and biological activity. Bile acids are now recognized not only as digestive detergents but also as signaling molecules that regulate secretion, absorption, intestinal motility, and mucosal homeostasis.

Bile acid receptors and motility

Bile acids influence gastrointestinal motility through receptors such as Takeda G protein-coupled receptor 5 (TGR5) and Farnesoid X receptor (FXR). A pivotal study showed that TGR5 mediates the prokinetic actions of intestinal bile acids and is required for normal defecation in mice [10]. In a related mechanism, bile acid signaling has also been shown to regulate basal and cholinergic-induced secretory responses in the colon [11]. Together, these findings indicate that bile acids affect both propulsion and stool hydration.

From a pathophysiological perspective, reduced colonic exposure to active bile acids may contribute to slower transit and harder stools. This mechanism is highly relevant to constipation because it integrates microbial metabolism, epithelial secretion, and motility within a single signaling axis.

Translational relevance of bile acid signaling

Bile acid-targeted therapy represents one of the clearest examples of microbiota-metabolite biology translated into clinical practice. Elobixibat, an ileal bile acid transporter inhibitor, increases bile acid delivery to the colon. A recent clinical study showed that elobixibat increases fecal bile acid concentration and shortens colonic transit time in chronic constipation [12]. This translational consistency strengthens the case for bile acid dysregulation as a mechanistic contributor to constipation rather than a secondary epiphenomenon.

Tryptophan-derived metabolites: Indoles and tryptamine

Tryptophan metabolism as a microbiota-host interface

Tryptophan metabolism lies at the intersection of microbial activity, epithelial signaling, immune regulation, and serotonin biology [13]. Gut bacteria convert tryptophan into a variety of bioactive molecules, including indoles, indole derivatives, and tryptamine. These metabolites influence mucosal signaling pathways that are relevant to intestinal motility and barrier function.

Tryptamine and epithelial secretion

A landmark study demonstrated that microbiota-produced tryptamine activates epithelial 5-Hydroxytryptamine receptor 4 (5-HT_4) receptor signaling, increases colonic anion and fluid secretion, and accelerates gastrointestinal transit [14]. This is particularly relevant to constipation, where reduced fluid secretion contributes to hard stools and delayed passage. Rather than acting as a generic fermentation product, tryptamine behaves as a highly specific microbial signaling molecule capable of promoting transit.

The therapeutic importance of this pathway is reinforced by evidence that epithelial 5-HT_4 receptors are promising targets for the treatment of constipation [15]. Taken together, these findings suggest that altered microbial tryptamine production may influence bowel habits through epithelial secretory mechanisms.

Indoles and AHR signaling

Indole derivatives also appear to regulate intestinal motility. A recent study showed that colon-targeted delivery of indole-3-acetic acid improves gut motility through activation of the aryl hydrocarbon receptor (AHR) [16]. Beyond motility alone, AHR signaling contributes to epithelial integrity and immune homeostasis. Thus, microbial tryptophan metabolism may affect constipation through a combined network of serotonergic, immune, and barrier-related pathways.

Methane and microbial gas metabolism

Among microbial gases, methane has the strongest association with constipation. Methane is produced primarily by methanogenic archaea, especially *Methanobrevibacter smithii*, and has repeatedly been linked to slow-transit states [17]. Experimental work demonstrated that methane slows intestinal transit and

augments contractile activity in a manner consistent with nonpropulsive motor effects. This suggests that methane may impair coordinated forward movement rather than simply suppressing muscle activity.

Clinical studies further support this relationship. Methane producers have been reported to exhibit prolonged colonic transit compared with nonproducers [18]. Although breath methane testing is not a perfect biomarker, it may help identify a constipation subgroup characterized by methanogen overactivity. This phenotype likely differs from constipation driven primarily by reduced SCFA production or altered bile acid signaling, underscoring the need for mechanistically informed subclassification.

Mechanistic pathways linking microbial metabolites to motility

Enterochromaffin cells and serotonin

The gut microbiota strongly influences serotonin biology. The study by Reigstad et al. established that microbial metabolites stimulate enterochromaffin cells and increase colonic serotonin production. Because serotonin initiates propulsive reflexes and facilitates secretion, this pathway provides a direct mechanistic link between impaired fermentation and constipation. Tryptamine extends this concept by activating epithelial 5-HT_4 signaling and enhancing secretory function.

Enteric nervous system and neuromuscular control

Microbial metabolites also modulate the enteric nervous system, which coordinates propulsion, segmentation, and reflex activity. SCFAs, bile acids, and tryptophan-derived metabolites may influence neuronal excitability either directly or through enteroendocrine intermediates. Although human mechanistic data remain limited, this framework is supported by experimental studies and provides one of the most plausible pathways through which microbial metabolism affects intestinal transit.

Epithelial secretion and stool hydration

Constipation is not solely a motility disorder; it is also a disorder of luminal hydration. Bile acids promote colonic secretion through receptor-mediated pathways, whereas tryptamine enhances epithelial fluid secretion through 5-HT_4 signaling. When these prosecretory influences are reduced, stools become drier and more difficult to pass. This helps explain why some therapies improve bowel habits even when their primary action is on secretion rather than on smooth muscle contraction.

Barrier and immune pathways

Microbial metabolites also regulate mucosal immunity and epithelial barrier function. Indole derivatives acting via AHR, as well as SCFAs such as butyrate, may restrain low-grade inflammation and preserve mucosal homeostasis. Because inflammation and barrier dysfunction can alter enteric neuronal responsiveness and smooth muscle behavior, these immune-modulatory effects may contribute indirectly to constipation pathophysiology.

Therapeutic implications

Diet and fermentable substrates

Dietary modulation remains a cornerstone of constipation management. Recent dietary guidelines provide evidence-based recommendations for adults with chronic constipation and reinforce the value of individualized fiber and food-based strategies. Mechanistically, such interventions may increase fermentable substrates for SCFA production and partially restore a more favorable intestinal metabolite environment.

Probiotics and synbiotics

Probiotics-containing products may improve constipation by altering microbial metabolism rather than by globally transforming microbial composition. A recent systematic review and meta-analysis found that probiotics-containing products increased stool frequency, improved stool consistency, and alleviated symptoms in adults with functional constipation [19]. An earlier meta-analysis also supported modest benefits, although heterogeneity among strains and study designs remained substantial [20]. These findings suggest therapeutic potential, but they do not yet support a universal recommendation for all patients.

Fecal microbiota transplantation

FMT is conceptually attractive because it transfers the metabolically functional microbial ecosystem rather than a single strain. A recent systematic review and meta-analysis concluded that FMT may improve symptoms and modulate gut microbial dynamics in adults with chronic constipation, although study quality and protocol heterogeneity remain major limitations. FMT should

therefore be regarded as promising but not yet standardized therapy for constipation.

Bile acid-targeted treatment

Among metabolite-oriented strategies, bile acid modulation has perhaps the strongest mechanistic rationale. Current guidelines recognize ileal bile acid transporter inhibitors as therapeutic options in selected patients. Elobixibat is especially relevant because its clinical efficacy aligns closely with experimental evidence that bile acids promote secretion and transit through receptor-mediated pathways.

Toward metabolite-informed precision therapy

Future treatment is likely to move beyond general microbiota modulation toward metabolite-guided precision strategies. Patients with reduced SCFA production, altered bile acid profiles, defects in tryptophan metabolism, or methane-dominant dysbiosis may not respond optimally to the same intervention. Integrating metabolomics with transit phenotyping may therefore help personalize dietary, microbial, and pharmacologic therapy.

Challenges and future directions

Despite major advances, several limitations remain. Much of the current human evidence is cross-sectional, making it difficult to determine whether altered metabolites are causes or consequences of delayed transit. Constipation is also clinically heterogeneous, and metabolite signatures likely differ across slow-transit constipation, normal-transit constipation, and evacuation disorders. In addition, stool metabolomics may not fully capture the spatial distribution of metabolites at the mucosal interface where many signaling events occur.

Future studies should combine rigorous phenotyping, longitudinal sampling, transit testing, and interventional metabolomics. More importantly, researchers should increasingly focus on functional pathways rather than merely cataloging microbial taxa. The most clinically relevant question is not only which microbes are present, but which metabolites are deficient, excessive, or dysregulated and how those changes alter host motor physiology.

Conclusion

Gut microbiota-derived metabolites are emerging as central regulators of intestinal motility in constipation. SCFAs connect microbial fermentation to serotonin biosynthesis and epithelial physiology. Bile acids link microbial biotransformation to secretion and prokinetic receptor signaling. Tryptophan-derived metabolites such as tryptamine and indole-3-acetic acid bridge microbial metabolism with 5-HT_4- and AHR-dependent pathways relevant to intestinal motility. Methane identifies a clinically relevant slow-transit phenotype associated with altered motor function. Together, these pathways provide a more mechanistic understanding of constipation than microbial taxonomy alone and support the development of metabolite-informed therapeutic strategies.

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Conflicts of Interest

The authors declare no conflict of interest.

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