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Gut bacteria ammonia production restores acetylcholine neurotransmission and bowel motility

Acetylcholine levels are reduced in gut dysmotility conditions. We find that gut acetylcholine levels induce a compensatory increase in gut microbiota urease activity and ammonia production. By upregulating presynaptic Cav2.1 calcium channels in enteric neurons, ammonia enhances calcium influx and restores acetylcholine release neurotransmission, revealing a microbiota-driven mechanism that preserves gut motility.

This is a summary of:
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The problem

Intestinal motility disorders, such as chronic constipation, are common conditions marked by slow gut transit and impaired enteric nervous system (ENS) activity. Acetylcholine (ACh) is the main excitatory neurotransmitter that drives peristalsis, and decreased ACh levels resulting in reduced cholinergic signalling is consistently observed in patients with chronic constipation. Whether declining ACh levels are compensated for to preserve motility remains unclear.

The gut microbiota is a key ENS modulator, as depletion disrupts neuronal excitability and slows transit, whereas reconstitution restores gut neuromuscular function[1]. Ammonia, a major microbial metabolite historically considered a neurotoxin, can also have beneficial roles, including maintaining brain glutamine to buffer stress and modulating enteric neuromuscular circuits via glial γ-aminobutyric acid (GABA) signalling[2,3]. Whether gut ammonia acts as an adaptive microbial signal that influences host intestinal physiology through specific enteric circuits has not been systematically investigated.

The discovery

To investigate whether gut microbes actively compensate for impaired enteric cholinergic signalling, we combined disease modelling, multi-omics profiling, microbial and microbiota manipulation, and mechanistic validation across in vivo, ex vivo and cellular systems. We used a mouse model of intestinal dysmotility induced by loperamide (an agonist of μ-opioid receptors in the myenteric plexus of the large intestine) to establish a controlled, reversible reduction in ACh-dependent motility. We used metagenomic sequencing, targeted metabolite quantification and analysis of public cohorts of patients with constipation to identify microbial metabolic pathways that are associated with dysmotility and not a direct effect of loperamide. We found that reduced ACh signalling during intestinal hypomotility consistently triggered a compensatory increase in microbial urease activity and ammonia production (Fig. 1a) in mouse models, attributed to an increased abundance of *Lysinibacillus fusiformis* (Fig. 1b), and in patients with constipation.

We tested the functional relevance of this urease activity by pharmacological inhibition, supplementation with urease-positive bacteria, administration of engineered microbial strains and controlled ammonia administration. Inhibition of microbial urease exacerbated dysmotility, whereas supplementation with urease-positive bacteria (Fig. 1c), engineered urease-expressing strains or physiological levels of ammonia rescued peristalsis without inducing systemic toxicity (Fig. 1d). To directly link microbial nitrogen metabolism with enteric neuronal activity, we performed intestinal transit assays, organ bath recordings, transcriptomics, and protein analyses.

Ammonia increased presynaptic Cav2.1 expression in enteric neurons, promoting Ca^{2+} influx and ACh release. Rather than a toxic byproduct, microbially derived ammonia enhances enteric neuronal excitability and restored colonic ACh levels, thereby improving intestinal motility.

Future directions

Our study reveals that the gut microbiota dynamically compensates for impaired enteric neurotransmission, linking microbial nitrogen metabolism to host intestinal motility. These findings establish microbial urease activity as a potential target for physiological modulation or targeted supplementation (using urease-positive bacteria), representing a novel avenue for treatment of constipation and other gut dysmotility disorders. Microbiota-derived metabolites might also act as adaptive feedback signals in other organ systems that are regulated by neural or chemical signalling, highlighting the broader importance of host–microbe metabolic interactions in maintaining systemic physiological homeostasis.

Although our findings are exciting, several limitations should be acknowledged. Microbial compensation alone does not fully reverse chronic dysmotility, particularly when structural or neuronal deficits exist. We relied on mouse models and limited human stool samples in our study, and interindividual differences in microbiota composition, urease abundance and ammonia tolerance could influence translatability. Moreover, the long-term safety of manipulating ammonia levels or introducing urease-positive bacteria in the gut remains untested. Finally, the precise molecular regulation of Cav2.1 trafficking and the involvement of post-translational modifications requires further mechanistic clarification.

In the future, we will investigate the long-term efficacy and safety of microbial or ammonia-based interventions in larger, more diverse cohorts. We will also explore how ammonia modulates Cav2.1 dynamics and signalling in glia, and whether other urease-positive gut microbial taxa can similarly sustain enteric neurotransmission under pathophysiological conditions.

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EXPERT OPINION

"This study provides an alternative explanation for high ammonia production during longer gut transit time. The insight that high bacterial urease enzyme activity and not a general increase in proteolytic activities is responsible for high ammonia production is exciting and novel. Moreover, the suggestion that bacterial ammonia production could serve as an active protective mechanism employed by the bacteria, which can elevate colonic ACh levels during constipation, is a paradigm shift in our understanding of transit time and bacterial metabolism in the gut." **Anurag K. Sinha, Technical University of Denmark, Kgs Lyngby, Denmark.**

FIGURE

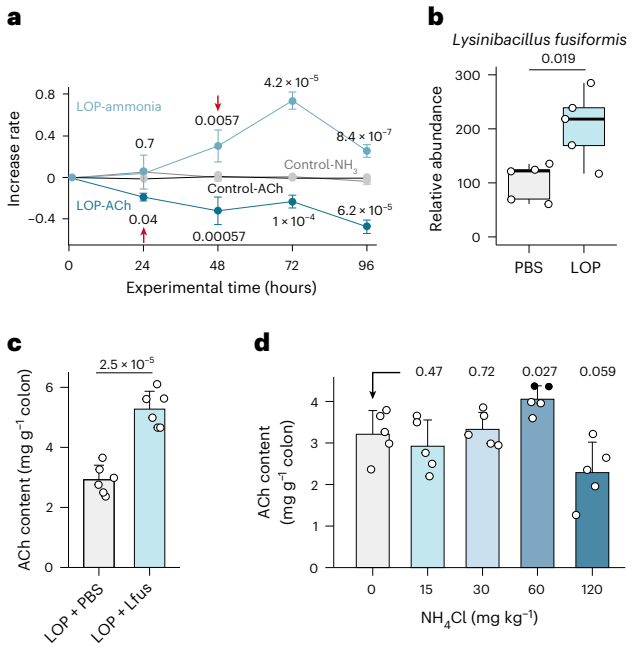


Fig. 1 | Microbial ammonia compensates for ACh deficiency. **a**, Time course of colonic ACh levels (dark blue) and faecal ammonia concentrations (light blue) in untreated mice or mice treated with loperamide (LOP) for 4 days. Red arrows indicate when group trajectories start to diverge significantly. **b**, Differential abundance of *L. fusiformis* in untreated mice (PBS) and mice treated with LOP. **c**, Changes in colonic ACh concentration in LOP-treated mice supplemented with or without *L. fusiformis*. **d**, Dose–response effect of NH_4Cl supplementation on colonic ACh levels. Data are mean ± s.d., except for in **b** (line, median; box limits, 25th and 75th percentiles; whiskers, Tukey's method (1.5× interquartile range)). Statistical significance assessed using two-tailed Student's *t*-test. © 2026, Chen, H. et al.

BEHIND THE PAPER

Our curiosity about how gut microorganisms shape intestinal motility began with a clinical phenotype: some patients with chronic constipation had elevated faecal ammonia despite slow transit. Early funding was tough, because the idea that microbial nitrogen metabolism could have a compensatory role was unconventional, but pilot data gradually convinced grant reviewers. Unexpectedly, we discovered that the urease-positive gut bacterium *L. fusiformis* could dramatically restore ACh levels in mouse models of dysmotility, which shifted our focus from broad microbiota effects to specific metabolic pathways. The breakthrough came when we showed that ammonia upregulates Cav2.1 in enteric neurons, directly linking gut microbial metabolism to neurotransmission. The most challenging phase was fine tuning ammonia dosing — enough to restore motility but not too much to cause toxicity. Seeing consistent physiological doses normalize colonic function was a true eureka moment. **H.C. & Z.Y.**

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   This paper reports that endogenous ammonia can beneficially modulate neurotransmitter pathways, highlighting its physiological roles beyond toxicity.

FROM THE EDITOR

"Intestinal transit time is one of the most important factors that determine the gut microbiota composition, but many people suffer from intestinal motility disorders. Therefore, it was quite interesting to see that gut microbes sense dysmotility and promote a compensatory mechanism that could be harnessed in the future for improved therapeutics." **Atin Sharma, Senior Editor, *Nature Microbiology*.**