Medium-chain Fatty Acids as Modulators of Microbial Ammonia Production and Metabolism in the Human Gut

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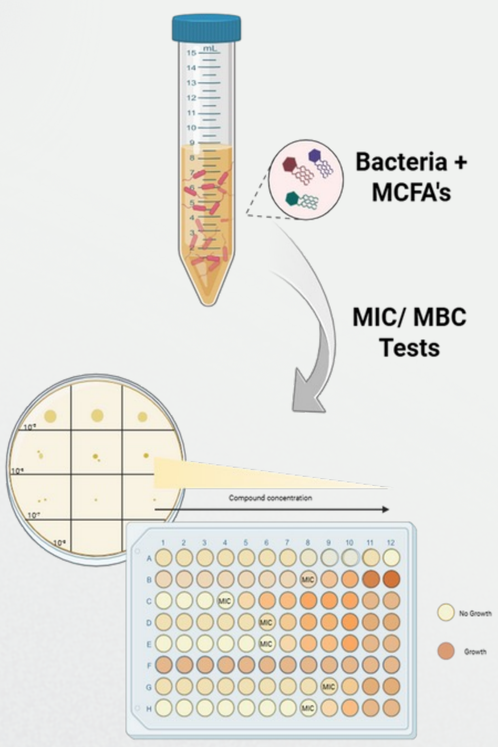
Introduction

Background:
Ammonia is a neurotoxic metabolite that plays a key role in the progression of hyperammonaemia, a condition marked by elevated systemic ammonia levels. In individuals with liver dysfunction, such as those with hepatic encephalopathy (HE), impaired detoxification allows ammonia to accumulate and cross the blood–brain barrier, leading to cognitive impairment, motor dysfunction, and potentially coma. Beyond HE, hyperammonaemia is also implicated in chronic kidney disease, muscle wasting, and neurodevelopmental complications. Inborn errors of metabolism, such as urea cycle disorders, result in defective ammonia clearance, where additional gut-derived ammonia may worsen the systemic burden.
Although the liver and kidneys detoxify ammonia, the gut microbiota is a major contributor to its production. In the colon, ammonia is primarily generated through microbial urease activity and amino acid deamination. Urease-positive bacteria convert urea into ammonia, significantly increasing the nitrogen load entering the portal circulation. Despite its clinical relevance, therapeutic strategies that directly target microbial ammonia production remain limited.
Medium-chain fatty acids (MCFAs), including caproic (C6), heptanoic (C7), octanoic (C8), and capric acid (C10), are saturated fatty acids with known antimicrobial and metabolic-modulating properties. These compounds can disrupt bacterial membranes, alter growth dynamics, and influence core metabolic pathways. Their potential to modulate microbial nitrogen metabolism positions them as promising candidates for reducing gut-derived ammonia. Lauric acid (C12), while structurally similar, is considered a long-chain fatty acid but remains of interest for its distinct biological activity.
Understanding how these nutrient-derived lipids affect microbial ammonia production may support the development of microbiome-based strategies for managing systemic hyperammonaemia across a range of clinical contexts.

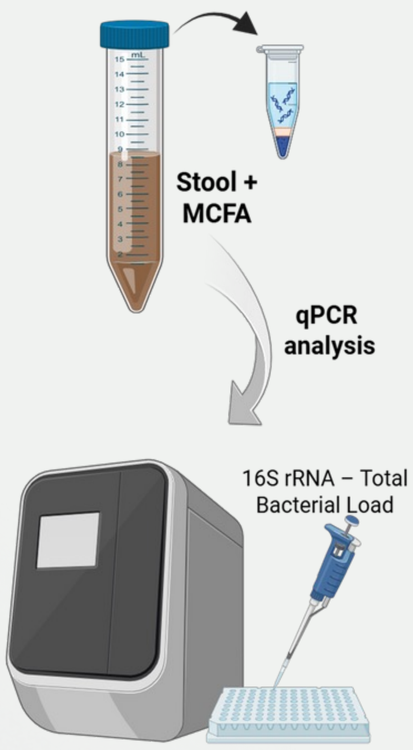
Aims:
This study investigates the potential of medium-chain fatty acids (MCFAs) to modulate microbial ammonia metabolism within the human gut microbiota. The focus is on four saturated fatty acids with known bioactivity: caproic acid (C6), heptanoic acid (C7), octanoic acid (C8), and capric acid (C10). The work aims to evaluate how these compounds influence bacterial growth, ammonia-related gene expression, and nitrogen output, using both defined bacterial isolates and fecal microbial communities.

Methodology

MCFA Effects on Ammonia-Producing Bacteria

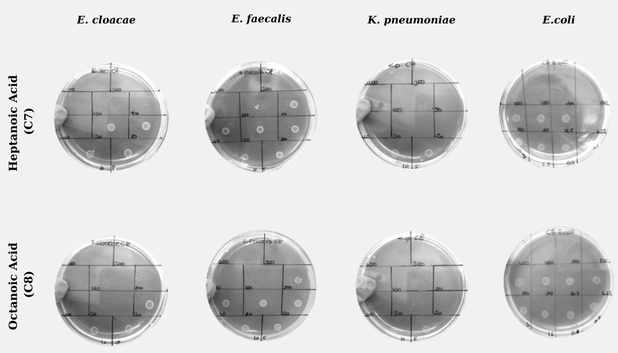


Molecular Impact on Bacterial Abundance



Results

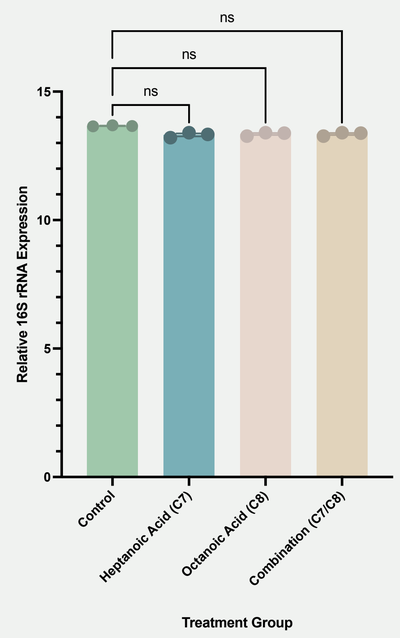
MCFAs Exhibit Antibacterial Activity Against Ammonia-Producing Bacteria



	C7		C8	
	MIC (mM)	MBC (mM)	MIC (mM)	MBC (mM)
E. coli	20	100	20	100
K. pneumoniae	5	20	5	20
E. faecalis	50	200	30	100
E. cloacae	5	40	5	30

Minimum inhibitory (MIC) and bactericidal (MBC) concentrations of heptanoic acid (C7) and octanoic acid (C8) against selected gut bacteria. K. pneumoniae and E. cloacae showed highest susceptibility (MIC: 5 mM).

Total Bacterial Load Remains Stable Following Treatment



Relative 16S rRNA gene expression in total bacterial DNA after treatment with heptanoic acid, octanoic acid, and their combination. Values are normalized to the control group and shown as mean ± SEM (n = 3). *$p < 0.05$ vs. control (One-way ANOVA, Tukey's test).

Conclusion

Medium-chain fatty acids (MCFAs), particularly heptanoic acid (C7) and caprylic acid (C8), demonstrated selective antibacterial activity against high ammonia-producing gut bacteria such as Klebsiella pneumoniae and Enterobacter cloacae. These effects were evident in reduced bacterial viability, supporting the potential of MCFAs as targeted modulators of microbial contributors to gut-derived ammonia.
MCFAs represent a promising non-antibiotic approach to influence microbial nitrogen output by suppressing key taxa involved in excessive ammonia production. This strategy aligns with emerging microbiome-based therapeutic frameworks aimed at addressing systemic complications of hyperammonaemia, particularly in conditions like hepatic encephalopathy and chronic kidney disease.
Future work will assess MCFA effects within fecal slurry models to better reflect the complexity of microbial communities. These experiments aim to evaluate shifts in total bacterial abundance and microbial composition, as well as potential impacts on metabolite production. Additional studies will include cytotoxicity screening to ensure host safety and compatibility, laying the groundwork for further translational research into microbiome-targeted ammonia control strategies.

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