Gut microbial metabolites lower blood pressure in patients with hypertension

Supplementation with the gut microbial-derived metabolites acetate and butyrate has been shown to lower blood pressure in experimental models of hypertension. However, the translational potential of these metabolites has been unexplored. We provide clinical evidence that acetate and butyrate lower blood pressure in untreated patients with hypertension.

This is a summary of:
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The question

High blood pressure, also known as hypertension, is one of the leading causes of death worldwide. Although clinical and lifestyle strategies are available, four out of five patients with hypertension continue to have uncontrolled high blood pressure, indicating that new interventions are needed. Over the past decade, mounting experimental evidence has shown that the gut microbiota and their metabolites contribute to the regulation of blood pressure. A key modulator of the gut microbiota is dietary fiber, particularly fermentable fiber, which is digested in the large intestine by commensal gut microorganisms, leading to the release of short-chain fatty acids (SCFAs)[1]. SCFAs are bioactive molecules that participate in several pathways controlling host physiology. Notably, studies have demonstrated that SCFA supplementation lowers blood pressure in experimental animal models[2]. However, no direct translational evidence has been reported using gut microbial metabolites to treat human hypertension.

The solution

The addition of acetate and butyrate — two microbial-derived SCFAs — to the drinking water of mice lowered blood pressure[2]. However, this mode of delivery is not feasible in humans, as it would require patients to constantly drink SCFAs throughout the day and night. To overcome this, we used acetylated and butyrylated high amylose maize (HAMSAB) — a fermentable fiber engineered to deliver sustained high levels of acetate and butyrate. We recruited 20 untreated hypertensive individuals to participate in a double-blind, placebo-controlled, randomized cross-over phase 2 trial to test the use of HAMSAB to reduce blood pressure over a period of 3 weeks. We measured 24-hour blood pressure and plasma SCFAs, and investigated the fecal microbiome, gastrointestinal transit and pH, and circulating cytokines.

In patients with hypertension treated with HAMSAB, we observed a 6.1 mmHg reduction in 24-hour systolic blood pressure compared with the placebo group (Fig. 1a). We also observed significant reductions in both average day and night systolic blood pressure. Further analyses revealed that plasma acetate and butyrate were significantly increased after the 3-week intervention with HAMSAB relative to the placebo arm (Fig. 1b). Moreover, HAMSAB shifted the gut microbial composition and increased the prevalence of producers of acetate and butyrate such as *Ruminococcus gauvreauii*.

The implications

Our findings suggests that the gut microbial metabolites acetate and butyrate lower blood pressure and, thus, might have therapeutic potential. This is in line with previous clinical[3] and experimental evidence[4] showing that perturbations of the gut microbiota, specifically the depletion of producers of SCFAs, may predate the development of hypertension. Thus, fermentable fibers such as HAMSAB might be used to restore gut microbial communities that support the production of SCFAs. In the future, this strategy may help to alleviate the global health burden of hypertension and associated cardiovascular disease.

A paucity of SCFA producers might impair crucial SCFA-dependent blood pressure regulating pathways, such as signaling via the G-protein-coupled receptor GPR43 (ref. [3]). Lack of signaling via GPR43 and other SCFA-receptors with anti-inflammatory properties[5] may be an underappreciated contributor to the development and maintenance of hypertension. Thus, restoring critical microbial taxa that produce SCFAs could be an important therapeutic goal for more optimal blood pressure control.

Although our study demonstrates the blood pressure-lowering effect of HAMSAB, multi-center trials with a larger sample size and longer-term follow-up will yield more conclusive results. Importantly, such a study would provide more insight into the large-scale feasibility of gut microbial strategies to treat hypertension. Further investigations might reveal the proportion of patients with hypertension amenable to this therapeutic approach and identify super-responders that could benefit from HAMSAB treatment.

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EXPERT OPINION

"The main limitation of this randomized trial was the small sample size. However, the fact that the authors observed differences in their primary outcome despite only having 20 participants suggests that the effects of their intervention are quite strong and clinically significant." **Noel T. Mueller, John Hopkins, Baltimore, MD, USA.**

FIGURE

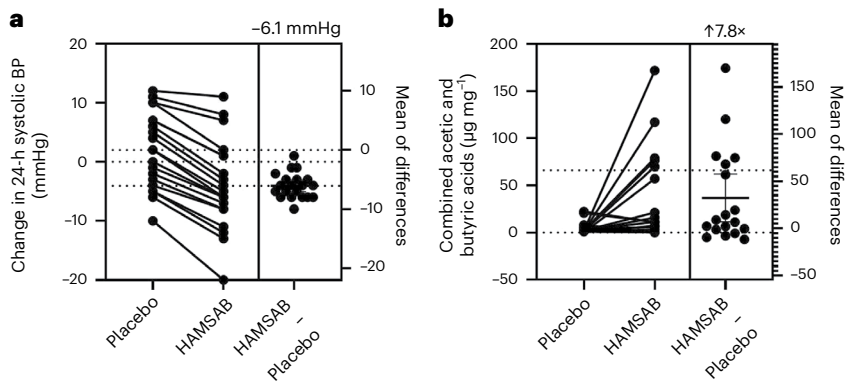

Fig. 1 | Lowing blood pressure by supplementation with HAMSAB. a,**b**, An acetylated and butyrylated high amylose maize (HAMSAB) intervention lowered 24-hour systolic blood pressure (BP) (**a**) and increased the levels of the short-chain fatty acids (SCFAs) acetate and butyrate (**b**) compared with placebo. Each data point represents an individual participant. © 2023, Jama, H. A. et al.

BEHIND THE PAPER

After observing the power of acetate and butyrate to lower blood pressure in our experimental models[2], we (F.Z.M., D.M.K. and C.R.M.) received a Vanguard grant from the National Heart Foundation of Australia to run this clinical trial. However, we then faced two major obstacles. The most obvious challenge was recruiting participants during the COVID-19 pandemic, particularly in Melbourne where we had 262 days of lockdowns across 2020–2021. Second, to ensure compliance, we engaged with dietitians (D.R.J. and J.M.) and a research chef (T. Veitch) to develop foods containing both HAMSAB and the placebo that tasted nice and were similar to each other so participants would remain blinded to which arm they were in — that helped us to ensure 93% compliance across both arms. This was a major undertaking and resulted in about 2,000 meals cooked for the trial! **H.A.J. & F.Z.M.**

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FROM THE EDITOR

"This phase 2, randomized, placebo-controlled double-blinded cross-over trial shows that an enriched high amylose maize starch is a safe and effective way to deliver short fatty acids, which are beneficial for systolic blood pressure reduction in patients with hypertension." **Elvira Forte, Associate Editor, *Nature Cardiovascular Research*.**