PERSPECTIVES ON RECENT STUDIES IN HYPERTENSION

Using gut microbial metabolites to lower blood pressure of hypertensive patients

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In January 2023, we published the results of the Microbial Interventions to Control and Reduce Blood Pressure in Australia (MICRoBIA) trial in Nature Cardiovascular Research,[1] where we reported the use of gut microbial metabolites to lower blood pressure (BP) of untreated essential hypertensive patients.

Dietary fibre, particularly fermentable fibre, is a key determinant of the gut microbiome.[2] Commensal gut microbes in the large intestine break down fermentable fibre, producing metabolites known as short-chain fatty acids (SCFAs).[3] Studies by our team[4,5] and others[6] have shown direct supplementation with the SCFAs acetate and butyrate decreased BP in deoxycorticosterone acetate (DOCA)/salt and angiotensin II mouse models. However, the ability of these gut microbial-derived metabolites to treat essential hypertension remained unknown. A major challenge in translating these findings was that, in animal studies, SCFAs are delivered in drinking water throughout the experimental protocol, which was not feasible in humans. Once-off shots of foods high in SCFAs, such as vinegar, were also not an option as they result in a peak of circulating SCFAs after 60 minutes but disappear after a couple of hours.[7] Thus, our biggest hurdle was figuring out a pragmatic and last-longing delivery system for SCFAs that was translatable to humans.

Our novel solution

To address these challenges, we used a fermentable fibre product where the SCFAs acetate and butyrate have been chemically added, called acetylated and butyrylated high amylose maise (HAMSAB). Similar to other types of fermentable fibre, HAMSAB remains intact as it reaches the large intestine. There, it undergoes fermentation by the gut microbiota, releasing high levels of acetate and butyrate.[1] An important property of HAMSAB is that it can be added to food products and consumed orally. Thus, we worked with a research chef and dietitians to develop a suite of foods that contained either HAMSAB or the placebo, including sweet and savoury muffins, frittatas and arancini balls.

What we found

We conducted a double-blind, randomised, placebo-controlled cross-over phase II trial involving 20 treatment-naive hypertensive participants over 3-weeks to test the efficacy of HAMSAB in reducing blood pressure.[8] Our participants were randomised into the HAMSAB-supplemented or placebo arm of the study, followed by a 3-week washout period before being placed on the other study arm.[8] We monitored BP at home and for 24 hours using ambulatory BP monitoring, measured plasma SCFAs, real-time

gastrointestinal transit and pH, and circulating cytokines. We also collected faecal samples from participants before and after each arm of the intervention to analyse their gut microbiota composition.[8]

We determined that HAMSAB resulted in a placebo-subtracted mean reduction of 6.1-mmHg in 24-hour systolic BP, with significant reductions observed in both day and night systolic BP, and central systolic BP.[1] Using home BP data, the BP reduction seems to peak at around 2-weeks after the introduction of HAMSAB.[1] This was associated with a reduction in calculated total peripheral resistance but no changes in stroke volume, cardiac output or heart rate.[1] Plasma acetate and butyrate levels were significantly elevated following the 3-week HAMSAB intervention compared to the placebo arm, as well as a decrease in colonic pH, which confirms SCFA production.[1] Furthermore, HAMSAB shifted gut microbial composition and transiently increased the prevalence of acetate- and butyrate-producing microbes such as Ruminococcus spp. and Parabacteriodetes spp.[1] These changes in microbiome composition were reversed back to baseline after 3-weels of washout when HAMSAB was stopped.[1] Given that SCFAs are anti-inflammatory, we looked at key plasma cytokines associated with hypertension (IL17A, IL1β, IL10 and IL6); however, we did not observe any differences between the HAMSAB and placebo.[1]

The implications

Our proof-of-concept study demonstrates that delivering gut microbial-derived metabolites using HAMSAB is a promising option for lowering BP in patients with essential hypertension. Combined with previous findings showing that untreated hypertensive patients have lower levels of SCFA-producers,[9] our findings suggest the absence of SCFA-producers may impair critical SCFA-dependent BP regulating pathways, such as signalling via the G-protein coupled receptors.[3] Recent evidence has shown a lack of signalling via classic SCFA receptors (e.g., GPR41/43)9,10 and pH-sensing receptors (e.g., GPR65)11 contribute to the development and maintenance of hypertension. Thus, restoring critical microbial taxa that produce SCFAs could be an important therapeutic goal for more optimal BP control.

Although our study demonstrates the BP-lowering effect of HAMSAB, we acknowledge that multi-centre trials with larger sample sizes 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 may reveal the proportion of hypertensive patients amenable to this therapeutic approach and identify super-responders that may benefit from HAMSAB supplementation.

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