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Gut Microbiota Modulation: Akkermansia muciniphila Lowers Blood Pressure by Restoring Serotonergic Gut-Vagal Signaling in Rodents

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Background: The gut microbiome is essential in maintaining overall host health including effects on blood pressure, metabolism, and neural signaling. An imbalance in gut microbiota has been linked to hypertension, but specific mechanisms underlying host-microbiota interaction remain poorly understood.

Objective: Our recent study established a direct and causative link between gut dysbiosis associated with hypertension and reduced serotonergic vagal signaling from the colon, contributing to elevated blood pressure in rodents. However, the exact role of a specific gut bacteria in this context has yet to be elucidated.

Methods/Results: Using bacterial sequencing and real time PCR, we observed significantly decreased abundance of *Akkermansia muciniphila (A. muciniphila),* a beneficial human gut commensal, in rodent recipients of fecal microbiota transplant from spontaneously hypertensive rats (SHR). Interestingly, the reduced fecal abundance of *A. muciniphila* was also observed in a Microbiome in aging Gut and Brain (MiaGB) consortium cohort of hypertensive middle- and older- age adults compared to normotensive controls (~5-fold, $p<0.05$). This reduction was associated with elevated systolic blood pressure (~10-12mmHg) and diminished serotonergic vagal signaling via 5HT3a receptors (5HT3aRs) (2-fold, $p<0.05$) in rodents receiving the microbiota transplants from the SHR compared to those transplanted with normotensive controls. Conversely, daily administration of *A. muciniphila* (108 CFU) to SHR via oral gavage for 8 weeks significantly reduced systolic blood pressure, measured by radiotelemetry (by ~20mmHg, $p<0.01$), elevated colonic serotonin (by ~20ng/mg

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tissue, $p<0.01$) measured by ELISA, and real time PCR showed increased expression of vagal 5HT3aRs (~50%, $p<0.05$), with no significant changes in the gut bacterial composition and diversity.

Conclusion: This study highlights the potential for leveraging *A. muciniphila* as new therapeutics for alleviation of gut dysbiosis-associated hypertension via serotonergic vagal signaling from the gut.

Keywords: Bacteria ,Serotonin, Vagus, Blood Pressure, Gut Microbiota

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