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Gut Microbiota:

Potential for a Unifying Hypothesis for Prevention and Treatment of Hypertension

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Abstract

Despite major advances in pharmacological and device-based therapies, systemic hypertension (HTN) continues to be the major, modifiable risk factor for most cardiovascular disease and a leading cause of morbidity and mortality. Treatment resistant HTN (RH) is present in ≈15% to 20% of hypertensive patients, with few treatment options. These facts provide an opportunity to develop novel hypotheses to advance this field.

Keywords

biomarker; dysbiosis; gut microbiota; resistant hypertension; treatment

Over 60 years ago, Irvine Page[1] proposed a mosaic theory where interplay of multiple factors integrate to increase blood pressure (BP). This fostered establishment of cellular, molecular, and physiological mechanisms altered in HTN. However, how these diverse factors integrate to impair BP control remains a challenge. Furthermore, why some factors are prohypertensive in one individual and not in another, and where prohypertensive signals originate, remains an enigma.

In this Viewpoint, we propose that the gut and gut microbiota could be one missing link and provide a potential unifying concept. We summarize most recent evidence for involvement of gut microbiota in BP control and HTN. We present our thoughts on the current state and relevant knowledge gaps to be addressed to determine whether targeting gut microbiota and related pathology would be a next frontier in HTN therapeutics.

Are HTN or RH Associated With a Unique Gut Microbial Signature?

Gut dysbiosis and microbial functions contribute to pathological effects beyond the gastrointestinal system. Gut microbiota play a role in BP regulation, and gut dysbiosis has been observed in multiple animal models of HTN.[2–5] Our group was among the first to

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None.

document HTN-associated gut dysbiosis and an increased Firmicutes/Bacteroidetes ratio.[2,3] This was associated with a decrease in acetate- and butyrate-producing bacteria and an increase in the lactate-producing bacteria. High-fiber diet and acetate supplementation correct gut dysbiosis, increase the abundance of acetate-producing bacteria, and are associated with lower BP in DOCA-salt mice.[5] Stroke-prone spontaneously hypertensive rats exhibit gut dysbiosis, and fecal microbiota transplant (FMT) from stroke-prone spontaneous hypertensive rats to Wistar–Kyoto normotensive rats increases BP.[4] Furthermore, we noted that HTN is associated with profound pathological changes in the gut and increases brain–gut transmission in animal models of HTN.[6]

Microbial dysbiosis has also been observed in patients with high BP.[2,3] Interestingly, subjects with HTN or pre-HTN demonstrate similar characteristic changes in gut microbiota composition.[7] In a RH patient, antibiotic treatment resulted in BP under control with only an angiotensin-converting enzyme inhibitor, suggesting possible involvement of gut microbiota in the pathogenesis of RH as antibiotics alter gut microbiota.[8] Future work will be needed to determine whether a unique microbial signature in the gut, gut pathology, and increased brain–gut–bone marrow connection are present in patients with RH.

Could Gut Microbiota Act as a Vector to Transmit HTN Phenotype Among Family Members?

Family history is an important nonmodifiable risk factor for HTN, and multiple factors account for inheritance of HTN.[9] Is it possible that people with a HTN family history inherit their gut microbiota from their parents? Gut microbiota is more similar among family members versus those who are not related.[10] Furthermore, increasing evidence shows that signals derived from the microbiota can act as environmental determinants to regulate global histone acetylation and methylation in multiple tissues of the host.[11] There is growing support to suggest that gut microbiota and their products have the potential to modulate host epigenomics, and the role of host epigenomics in HTN is under investigation. Furthermore, HTN phenotype in microbiota can be transferred by FMT. For example, FMT from Dahl salt-sensitive rats to Dahl salt-resistant rats, from stroke-prone spontaneously hypertensive to Wistar–Kyoto normotensive rats,[4] and from hypertensive patients to germ-free mice all lead to increased BP.[7] It is likely that gut microbiota work, at least in part, as a vector to transfer hypertensive traits among family members. Thus, signals derived from microbiota may induce epigenetic changes in gut epithelial cells to alter gut wall permeability. This could initiate a series of altered signaling events involving endocrine, immune, and neural pathways adversely impacting the cardiovascular system, leading to an increase in BP and establishment of HTN. This hypothesis would provide the basis for individualized hypertensive response to prohypertensive stimuli. However, alternate possibilities of prohypertensive factors directly inducing epigenetic changes in gut epithelial cells, and in turn influencing the microbiota, cannot be discounted.

Could Bidirectional Influences Between Gut Microbiota and Antihypertensive Medications Contribute to Development and Progression of RH?

Bidirectional influences between gut microbiota and drug metabolism are important in HTN. Medications, including antibiotics, are known to profoundly affect gut microbiota, and similarly, the microbiota can affect drug pharmacokinetics.[12] Certain antihypertensives reduce gut smooth muscle contractility to cause constipation. Patients with constipation have significantly less lactate-producing bacteria and higher intestinal permeability and immune response versus controls. Recent recognition of the impact of gut microbiota on microbial transformation of drugs has led to a paradigm shift in drug design. Gut microbiota could influence the efficacy and toxicity of antihypertensive drugs in patients, and a recent study confirmed this cross talk relationship. Bioavailability of amlodipine is increased by antibiotic suppression of gut microbial metabolic activity.[13] This partially explained the decreased need for antihypertensive medications during and after antibiotic treatment in RH patients. Taken together, they raise an important question worthy of further investigation: is sensitivity/resistance to antihypertensive medication dependent on gut microbial composition? Is it possible that microbiota in resistant patients metabolize antihypertensive drugs at a faster rate? Are sex and race differences in BP control linked to differences in microbiota's ability to metabolize these antihypertensive drugs? Answers to these questions would be crucial in the development of a new generation of therapies.

Pre- and Probiotics as Possible Antihypertensive Agents

Pre-and probiotics modulate cholesterol, inflammation, blood glucose levels, and the renin–angiotensin system to lower BP and risk for HTN.[14] Manipulating gut microbiota using pre- and probiotics might prove a valuable adjuvant to traditional antihypertensives. A meta-analysis suggested that they may lower BP by a modest degree, with potentially greater effect when BP is elevated, multiple probiotic species are consumed, the duration is ≥8 weeks, or daily consumption is ≥1011 colony-forming units.[15]

Clearly, it is important to better understand the variability of gut microbiota across the population and how this variability relates to specific microbial functions. Specific probiotic species may be beneficial to some but not others. Almost 100% of Asian and African populations carry *Lactobacilli*, whereas *Lactobacilli* are rarely found in people living in Western societies.[16] However, a detailed understanding of gut microbial composition in relation to BP, ethnicity, and so on must be evaluated to fully appreciate the implications of pre- and probiotics in HTN therapeutics.

Knowledge Gaps and Recommendations to Address These Knowledge Gaps

We propose that both fundamental basic investigations and preclinical studies must continue to address the following:

1. Proof of concept that the brain–gut axis is dysfunctional in HTN needs to be firmly established. Initial evidence indicates that sympathetic nerve activity to gut increases before HTN development and dysbiosis.[6] Targeting gut sympathetic nerve activity would be an important option if this could be proven.
2. How do different HTN stimuli (eg, diet, salt, environment) influence gut microbiota and pathology? What are the mechanisms? Is it epigenetic influence on gut epithelial cells, bone marrow cells, sympathetic nerve activity, and so on?
3. Metagenomic studies are needed to include involvement of viruses, archea, and fungi.
4. Metagenomic studies are needed to investigate family, sex, race, and drug sensitivity/resistance in normal and hypertensive subjects. This will be critical in delineating unique microbial profile(s) linkage and would be valuable in FMT, pre- and probiotics, and antihypertensive therapies.
5. Is there a unique microbial DNA signature in blood linked to HTN? Increasing evidence suggests bacterial DNA in some chronic diseases with leaky gut and dysbiosis. Identification of such a signature may provide a novel biomarker for HTN development.
6. Metabolomic studies, focusing on microbiota-related metabolites, must be performed to investigate presence/absence of HTN-linked markers.
7. Investigation is needed on the heritability of microbiota-dependent epigenetic modifications and the possibility of using epigenome-targeting drugs or bacteriophages to restore the eubiosis and homeostasis.

In summary, our view is that the gut and its microbiota hold a central place in the mosaic theory.[1] They have potential to be a target of converging hypertensive stimuli and to disseminate diverse signals (eg, neural, endocrine, immune) to various cardiovascular-relevant organs to initiate HTN. Advances in bioinformatics, metabolomics, metagenomics, and metatranscriptomics provide convincing evidence linking gut dysbiosis to HTN in animal models and patients. However, caution is needed as many important questions remain unanswered. Heading the list is what exactly initiates attraction of certain gut microprobes to patients who will become hypertensive and develop RH. It would be important to establish metabolite and microbiota signatures that could be used to predict HTN development or biomarkers for RH. If we can alleviate HTN, even partially, with pre- and probiotic supplementation or FMT, the effects will be far-reaching.

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