

Gut micro biota, a rising star in hypertension

Abstract

Gut microbiota is previously a “forgotten organ”; growing evidence has elucidated their roles as a second genome in modulation the metabolic relevant disease. They contribute to decreasing hypertension and other cardiovascular diseases. Here, we summarize effects of microbiota on hypertension both in the animal model and human studies, its potential mechanisms and therapeutic prospects.

Keywords: gut microbiota, hypertension, short-chain fatty acid, fecal microbiota transplantation, probiotics

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Introduction

Hypertension is a prevalent condition and may have a significant impact on heart, brain, kidney which often lay an enormous burden on society and a low-level quality of lifestyle on the patient. The overall prevalence of hypertension has not changed since 2009-2010, the young adults still have lower awareness of their hypertension and 75percent people taken medicine to lower hypertension.¹ Hypertension may be either primary or secondary. For primary hypertension, 95% of all hypertensive cases was diagnosed with no known cause,² the known etiological factor is salt intake, obesity, insulin resistance, aging and perhaps sedentary lifestyle, stress, inherited BP.³ The regular therapy of hypertension control is the anti-hypertension drugs which often have the poor medication adherence and complications. As for white-coat hypertension, H-type hypertension, and resistant hypertension, the treatment is still intractable. Thus, diet modification or identifying new therapeutic targets that produce reductions in hypertrophy has considerable importance for public health. Gut microbiota, a forgotten organ in our organisms, its whole role was rarely reported and attracted attention in hypertension previously.

The microbiota in human intestinal tract

It is estimated that a number of the human microbiota is ten times higher than that human cells.⁴ And our intestinal tract is a nutrient-rich environment, containing huge numbers of microorganisms, up to 100 trillion, often called gut microbiota.⁵ The human intestinal microbiota is primarily dominated by the Bacteroidetes and the Firmicutes; other microbiota is present in the minor properties.⁶ Paul B Eckburg et al.⁶ improved understanding of gut microbial diversity and discovered that significant intersubject variability and differences between mucosa community composition and stool through the examining 13355 prokaryotic ribosomal RNA (rRNA) gene sequences from multiple colonic mucosal sites and feces of healthy subjects. Bing Han et al.⁷ have found that certain bacterial mutants promote host longevity and developing genetically engineered probiotics hold great promise for promoting healthy aging and as a new therapeutic paradigm.

Factors that regulate microbiota

Many factors could regulate microbiota, among them, the environmental factor, host genotype, age, health status, diet and so on are in hot discussion and research. Host genetic and multiple environmental control is in shaping individuality in gut microbiota composition, which is often a complex polygenic trait.⁸ Marcus J Claesson et al.⁹ demonstrate that gut microbiota composition strongly associated with diet and health in the elderly. They found that the microbiota composition was less diverse in the individual who was in long-stay care and significantly associated with the frailty, co-morbidity, nutritional status and so on. Exercise, an important role in host metabolism and immunity, is also a beneficial impact on microbiota diversity.¹⁰ With the complete of gene pool, 16S rRNA sequencing technology has been one of the forceful facilities for the gut microbiota.

The arisen approach of the gut microbiota analysed

The function of human gut microbiota has been analyzing by the different approach. Our knowledge about gastrointestinal bacterial diversity has increased accompanied by the development of the various molecular approaches such as fluorescent in situ hybridization, sequencing of 16S rDNA clones, DNA microarrays or, more recently, high-throughput sequencing.¹¹⁻¹⁵ For discovering of gut microbiota biodiversity, high-through-put sequences by means of Next Generation Sequencing (NGS) technologies has been the provital facilitating.¹⁶ As 16S ribosomal RNA(16S rRNA) subunit genes are highly conserved in bacterial species, they provide the most useful information of bacterial classification.¹⁷

Gut microbiota in cardiovascular diseases

Intestinal microbiota metabolizes the dietary phosphatidylcholine, and then product trimethylamine-N-oxide (TMAO), the increased level of TMAO are associated with an increased risk of an incident major adverse cardiovascular event.¹⁸ Zeneng Wang et al.¹⁹ also proved that gut flora metabolism of phosphatidyl choline deteriorates cardiovascular disease.

Elevated plasma TMAO, choline, and betaine levels are each correlated to more advanced left ventricular diastolic dysfunction and indicate poorer long-term adverse clinical prognosis in chronic systolic heart failure.²⁰ In the rat acute myocardial infarction (AMI) model, the abundance of gut microbiota was significantly higher than the sham group in the seven days after AMI, and the diversity of microbiota families have changed.²¹ And microbiota might also contribute to the morphology, permeability, and absorption of the intestinal tract in chronic heart failure. Higher concentration of adherent bacteria was found within mucus of the chronic heart failure patient compared to the control subjects.²² The microbiota plays an enormous role in cardiovascular disease, as for in hypertension regulation, its heavy responsibility will not be listed outside.

Microbiota and hypertension

Animal model

In the Dahl salt-sensitive (S) and Dahl salt resistant (R) rats model, 16S rRNA gene sequence detected that various phylogenetic groups of cecal microbiota revealed valid change between S and R rats model. And in the S rat given R rat's bolus of cecal content, systolic blood pressure (BP) elevated compared with the S rats given the cecal content from the S rat, which suggest that relation between the microbiota and host genome in the context of the BP regulation in the rat model.²³ A diet rich in fiber led to changes in the gut microbiota and thus prevent the development of hypertension. This change could be explained by the metabolism product of the gut microbiota, the short-chain fatty acid (SCFA).²⁴ The SCFA, primary acetate, propionate, and butyrate, is the endpoint product of the fermentation of dietary fibers by the anaerobic intestinal microbiota.²⁵ Absorbed by the gut epithelial cells, the SCFAs have substantial effects on the energy metabolism.²⁶ Butyrate is one of the SCFA too. Sodium butyrate has been found to play a protective role in some chronic diseases. And Wang L et al.²⁷ have found that sodium butyrate could reversal the Ang II induced renal injury, angiotensinogen, angiotensin I converting enzyme and so on. Even *in vitro* study, sodium butyrate treatment attenuates Ang II-induced expression of the (pro) renin receptor and renin. Jennifer L Pluznick et al.²⁸ found that SCFAs regulate BP through the receptor of Olfr78 and Gpr41. Olfr78, an olfactory receptor, expressed in the renal juxtaglomerular apparatus, could mediate the renin secretion when in response to SCFAs, thus up-regulating BP.

Whereas the Gpr41, expressed on the small resistant vessels, play the adverse role that of Olfr78. The classic example is the propionate, one of the SCFAs, produce an acute hypotensive response by differentially disrupting the Olfr78 and Gpr48.²⁸ Toll-like receptor 5 (TLR5), a component of the innate immune system, expressed in the gut mucosa, could help develop hallmark features of hypertension. The TLR-5 deficient mice exhibit obesity, hyperphagia and hyperglycemia/insulin resistant. Transferring the gut microbiota from the TLR-5 deficient mice to the wild-type germ-free mice is sufficient to transfer metabolic syndrome phenotype to the recipient.²⁹ Since exercise is a well-known agent used to treat hypertension, whether exercise therapy could affect the gut microbiota is unknown. Pyrosequencing of 16S rRNA from the fecal samples found that exercise training altered the composition and diversity of the gut microbiota even in all rat lineages.³⁰ The individual who is suffering from the obstructive sleep apnea (OSA) is at high risk for secondary

hypertension. OSA model rats fed a high-fat diet, blood pressure increases significantly, while the OSA with the normal diet one did not affect BP. Gut microbiota decrease OSA rats with the high-fat diet. Transplantation of the dysbiotic cecal content from hypertensive OSA with high-fat diet rats into the OSA in the normal chow diet rats resulting in the latter BP increasing.³¹ Gut receives significant sympathetic innervation. Monica M et al.³² demonstrated that in hypertension, the gut changed pathologically and associated with alterations in microbial communities. The dysfunction of sympathetic-gut communication is associated with gut pathology, dysbiosis and inflammation, last but not least, relevant to hypertension.

Human studies

One study in the cohort of healthy controls, pre hypertension, individuals with primary hypertension, through the metagenomic and metabolites analyze, found that dramatically decreased microbial richness and diversity in the pre hypertension and hypertension people. All of the prehypertension and hypertension host have the gut microbiome dysbiosis. Besides, transplanting the fecal of hypertension people on to the germ-free mice, the elevated BP was observed in the germ-free mice which could be the implication of the microbiota.³³ In spontaneous hypertension and Ang II infusion rat model, the microbiota richness was decreasing, and an increased Firmicutes/Bacteroidetes ratio transplantation. Similarly, hypertension patients follow a similar dysbiotic pattern. And the acetate- and butyrate-producing bacterial are expanded by the minocycline treatment.³⁴ In the pregnancy-induced hypertension women, the Study of Probiotics in Gestational Diabetes have also found that the abundance of butyrate and butyrate-producing bacteria in the gut oxide: with BP.³⁵

Possible mechanisms: how the gut microbiota regulating hypertension

The mechanisms of the microbiota's influence on the hypertension are still unclear. Accumulate evidence suggests that gut microbiota affect the cardiovascular system might mainly through the immune systems and the gut microbiota product such as SCFA and Hydrogen Sulfide (H₂S) and so on. Immune system could control the microbiota, and the microbiota is also an important factor in the shaping of the immunity.³⁶ The gastrointestinal tract is the primary site of interaction between the host immune system and microorganisms, both symbiotic and pathogenic.³⁷ SCFA produced by gut microbiota modulate hypertension mainly through the signal in opposition to each other: the receptor Gpr41 and Olfr78 as mentioned before. Propionate, one of the SCFA, activate the Gpr41 leads to a hypotensive response and enable the Olfr78 favors a hypertensive response via renin release mediated by cAMP production. However, these effects are abolished in Olfr78 and Gpr41- deficient mice, as well as an antibiotic-treated mice.³⁸ H₂S is also a microbiota metabolite, an important biological mediator involved in the various process include hypertension.³⁹ Lenka Tomasova et al.⁴⁰ found that intracolonic administration of Na₂S, an H₂S donor, the BP dose-dependently decreased. And the rats treated with neomycin, an antibiotic showed a tendency of hypotension, which suggest that gut-derived H₂S may be beneficial for the control of BP and be the link between the gut microbiota and hypertension. Most importantly, the cross-talk between the gut microbiota and the metabolism of renal, brain, endocrine could be relevant to the pathological process and treatment of hypertension.

Fecal microbiota transplantation (fmt) and therapeutic prospects

FMT is the transplantation of microbiota from a healthy donor into a recipient's intestinal tract, which results from the restoration of diversity and richness of the recipient's gut microbiota and conferring a health benefit, and is arguably thought to be the most efficient approach of treating recalcitrant *Clostridium difficile* infection.⁴¹ Over time the FMT was obsolete in consideration of the hygiene and ethical issue. Whether the FMT has the therapeutic implications is still confused. Identifying a single or combination of bacterial strains that might work for the FMT therapeutics.⁴² To overcome these barriers, further going study identify single or the combination of bacterial strains will work hopefully for the FMT. Because multiple diseases are related to the flora dysbiosis, that FMT might have a therapeutic perspective in the future.

Probiotics supplement and diet modulation as an application of microbiota in treatment of hypertension

Probiotics

Probiotics are viable microorganisms mainly colonized in the gut, ameliorate the host's health condition once consumed in appropriate amounts.² Among them, the *Lactobacillus* and *Bifido bacterium* are the most used probiotics in pharmaceuticals and foods.⁴³ Once SHR rats were long term administered with probiotics *Lactobacillus* fermented CECT5716 (LC40), or *L. hypertension: CECT5711* (K8) plus *L. gasseri* CECT5714 (LC9) (1:1), systolic BP reduced, improvement of vascular pro-oxidative and pro-inflammatory status reversed.⁴⁴ Lata Ramchandran et al.⁴⁵ also discover that feeding diets supplemented with yogurts can beneficially affect blood as it exhibited not only hypocholesterolemic but also antihypertensive effects in the SHR model. From a systemic review and meta-analysis conclusion, we found that probiotics consumption significantly changed systolic BP by -3.56mmHg and diastolic BP by -2.38mmHg compared with control groups. And greater reduction even found in the multiple apply than the single species of probiotics.⁴⁶ Probiotics are usually supplemented in the food in the form of yogurt, fermented milk or other fermented foods, which will fall into the lactic acid-producing bacteria in the organism.⁴⁷

Diet modulation

In the obesity hypertensive patients, a hypocaloric diet supplemented with a probiotics cheese helps to reduce BMI and arterial BP values in Russian adults.⁴⁸ The rats, adding the NOS inhibitor NG-nitro-L-arginine methyl ester (L-NAME) to induce the status of hypertensive, treated with the blueberries fermented with the tannase producing bacteria *L. Plantarum* DSM15313, BP decreased after two weeks of treatment.⁴⁹ A dose-response meta-analysis of prospective cohort studies suggests that low-fat dairy and milk could contribute to the prevention of hypertension. And total dairy, low-fat dairy, and milk were inversely and linearly associated with a lower risk of hypertension.⁵⁰ As is well known, that fiber is good for the gut, reports also suggest that a diet rich in fiber alter the gut microbiota population and increase the abundance of acetate-producing bacteria.²⁴ The beneficial effects of fiber might be explained by the generation and distribution of one of the primary metabolites of the gut microbiota, the SCFA.⁵¹

Conclusion and future prospective

Along with the development of the next generation of sequence, it has become increasingly apparent that microbiota is crucial in the crosstalk of the whole system and contribute to hypertension. Thus, they are a very promising target for the future treatment orientation to hypertension and other cardiovascular diseases, although present techniques for finding the specific and efficiently probiotics as the therapeutical application are relatively complicated. We believe that applying advancing technologies to gut microbiota intervention will soon lead to a development of improved methods and realize personalized and precise medicine. And even treating hypertension efficiently just start from the diet supplement of specific probiotics isn't a dream.

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Conflict of interest

Author declares that there is no conflict of interest.

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