Hypertension: microbiota-targeting treatment

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Hypertension, as the most common cardiovascular disease (CVD), occurs with a high morbidity. The disease attacked a population of about 1.13 billion in 2015 globally, and its prevalence exceeds 27.9% in Chinese aged >18 years.[1] Unfortunately, lifestyle modifications and medical interventions fail to control the disease in a third of patients. Human gut microbiota can regulate immunity, inflammation, and metabolism. For decades, increasing evidence has shown that the activity and composition of microbiota are related to health status (like influencing blood lipid and glucose), which provides a new insight into the mechanism of hypertension.[2,3]

Recent studies have found that the gut microbiota can monitor the blood pressure (BP) in a variety of ways. BP changes with the abundance or composition of gut microbiota. Short-chain fatty acids (SCFAs) exert direct effects on BP through acetate, propionate, butyrate or indirect effects through various cytokines. Trimethylamine oxide can be used as an indicator for BP.[3] Some studies have shown that single or combined use of probiotics can protect the heart against hypertension. Besides, fecal microbiota transplantation (FMT) has shown potential in treating hypertension. This paper sketches out the mechanism engaging hypertension and gut microbiota, enumerates the use of probiotics in the treatment of hypertension and discusses the prospect of FMT. We proposed the feasibility of modulating gut microbiota as novel therapeutic strategies except for oral antihypertensive drugs.

Probiotics derived from traditional fermented foods and beneficial symbiotic biomass have been proven to exert therapeutic effects on many diseases through restoring the gut dysbiosis.[4] Currently, rich evidence indicates that dysbacteriosis can increase the risk of hypertension.[3] Now, probiotics have not been widely used in clinical practice. Therefore, the efficacy of probiotics for CVDs needs to be validated in the future.

SCFAs (acetate, butyrate, propionate, and so on) are produced by the gut microbiota from indigestible polysaccharides and play an important role in BP. They are absorbed from the colon into the bloodstream to control metabolic and inflammatory responses. Adding propionate (200 mmol/L) into drinking water significantly inhibits myocardial hypertrophy, fibrosis, vascular dysfunction, and hypertension in angiotensin II infused wild-type Naval Medical Research Institute (NMRI) mice or gene knockout mice deficient in apolipoprotein E gene. BP reduction was observed in the late phase of angiotensin II infused wild-type NMRI mice, suggestive of the favorable effect of propionate on hypertension.[5] Recently, several studies have shown that kefir (a probiotic beverage) can significantly prevent atherosclerosis and reduce BP in mice. Oral gavage of kefir for 9 weeks reduced mean arterial pressure and normalized heart rate in spontaneously hypertensive rats (SHRs). This decrease is a joint outcome of the reduction of cardiac hypertrophy, the improvement of cardiac contractility and calcium-handling proteins, and the sympathetic activity enhanced by the central nervous system.[6]

Research on the relationship between *Lactobacillus* and hypertension is also inspiring. *Lactobacillus fermentum* CECT5716 (LC40) supplementation cannot inhibit hypertension induced by N_G-nitro-L-arginine methyl ester, but it can prevent gut microbiota imbalance, oxidative stress, vascular inflammation, T-helper type 17 (Th17)/regulatory T (Treg)-cell imbalance of mesenteric lymph nodes, and slightly improve the function of endothelial cells.[7]

Increasing animal studies show that probiotics can reverse the pathologic changes caused by gut microbiota disturbance. The same results have also been found in clinical trials.[8] It is arresting that probiotics are therapeutically effective in many metabolic diseases, such as diabetes and hyperlipidemia. In addition, the beneficial effects of probiotics on hypertension have also been discussed. Meta-analyses of the relationship between BP and probiotics have shown that supplementation with probiotics

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may be beneficial to hypertensive individuals via reducing BP or damage to target organs. Meta-analysis of 14 randomized placebo-controlled trials involving 702 participants showed that probiotic fermented milk posed antihypertensive effects on both pre-hypertension and hypertensive patients. These probiotics caused a reduction of 3.10 mmHg in systolic BP and 1.09 mmHg in diastolic BP.[9] Another meta-analysis not only suggested that consuming probiotics may improve BP, but also provides further information between the consumption of probiotic and BP. The BP may be improved obviously when baseline BP is elevated, multiple species of probiotics are consumed, the duration of intervention is 8 weeks, or daily consumption dose is $\geq 10^{11}$ colony-forming units. This meta-analysis found a greater reduction in multiple species of probiotics, a more obvious improvement in lower baseline BP, and a significant decrease in longer duration of intervention.[10]

On the other side, some experiments showed contradictory results. To delve into the efficacy of *Lactobacillus acidophilus* La5 and *Bifidobacterium animalis* subsp. *lactis* BB-12 on BP, a clinical study showed that compared with the control group, the efficacy of probiotic yogurt or capsules on BP was not significant, suggesting that probiotics did not counter cardiovascular risk factors.[11] Invalidity of host probiotics indicates that the selective microbiota should be used to treat heart diseases and hypertension.

FMT, the core therapy for remodeling the gut microbiota, has gained global attention in recent years. FMT can be traced back to 1700 year ago in China, and has been applied for *Clostridium difficile* infection, inflammatory bowel disease, neuron diseases, and metabolic diseases.[12] The potential of FMT in the treatment of CVDs is mainly investigated with animal experiments. In the mouse model of myocarditis, an obvious increase was observed in microbial richness and diversity and the Firmicutes/Bacteroidetes ratio.[13] The study showed that after experimental autoimmune myocarditis mice were treated with fecal contents of untreated male mouse, their myocardial damage was reduced, inflammatory infiltration inhibited, gut microbiota balanced, and the number of *Bacteroides* and the composition of gut microbiota restored.[13] In another study about hypertension mice, recipient normotensive Wistar-Kyoto (WKY) rat and SHR were orally given donor fecal contents from SHR and WKY. Then, the animals were divided into four groups: WKY transplanted with WKY microbiota (W-W), SHR with SHR (S-S), WKY with SHR (W-S), and SHR with WKY (S-W). It showed that the basal systolic and diastolic BP decreased after FMT from WKY to SHR, but the heart rate did not change significantly. Similarly, the basal systolic and diastolic BP increased after FMT from SHR to WKY.[14] At present, the treatment of hypertension by FMT was mainly tested in animal experiments, seldom in clinical studies. Therefore, more clinical studies should be carried out in the future to make it clear; moreover, we should also focus on the standardization and safety of this technology, for example, the controllable preparation process is needed to achieve "washed microbiota transplantation."[12,15]

In conclusion, gut microbiota is related to the occurrence of hypertension and its subtypes. The adjunctive effect of probiotics on BP is gradually revealed *in vivo* and *in vitro* now. Moreover, FMT is better than probiotics in improving gut microbiota function, so FMT should be expected and modified in the future. Microbiota-targeting treatment is promising for hypertension.

Conflicts of interest

None.

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