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Gut microbiota and hypertension: association, mechanisms and treatment

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ABSTRACT

Objectives: Hypertension is one of the most important risk factors for cardio-cerebral vascular diseases, which brings a heavy economic burden to society and becomes a major public health problem. At present, the pathogenesis of hypertension is unclear. Increasing evidence has proven that the pathogenesis of hypertension is closely related to the dysbiosis of gut microbiota. We briefly reviewed relevant literature on gut microbiota and hypertension to summarize the relationship between gut microbiota and hypertension, linked the antihypertension effects of drugs with their modulation on gut microbiota, and discussed the potential mechanisms of various gut microbes and their active metabolites to alleviate hypertension, thus providing new research ideas for the development of antihypertension drugs.

Methods: The relevant literature was collected systematically from scientific database, including Elsevier, PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), Baidu Scholar, as well as other literature sources, such as classic books of herbal medicine.

Results: Hypertension can lead to gut microbiota imbalance and gut barrier dysfunction, including increased harmful bacteria and hydrogen sulfide and lipopolysaccharide, decreased beneficial bacteria and short-chain fatty acids, decreased intestinal tight junction proteins and increased intestinal permeability. Gut microbiota imbalance is closely related to the occurrence and development of hypertension. At present, the main methods to regulate the gut microbiota include fecal microbiota transplantation, supplementation of probiotics, antibiotics, diet and exercise, antihypertensive drugs, and natural medicines.

Conclusions: Gut microbiota is closely related to hypertension. Investigating the correlation between gut microbiota and hypertension may help to reveal the pathogenesis of hypertension from the perspective of gut microbiota, which is of great significance for the prevention and treatment of hypertension.

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Introduction

Hypertension is not only a global public health problem but also the most important risk factor for cardiovascular diseases, bringing a heavy economic burden to the society. The epidemiology of hypertension is characterized by high incidence, high disability rate, high mortality rate, and low awareness rate (1) (2). In 2021, about 330 million people are suffering from cardiovascular diseases in China, in which 245 million people are hypertensive patients (3). As the most important risk factor, control of blood pressure has been deemed as an essential method to prevent the incidence of cardiovascular diseases. Currently, available drugs for the treatment of hypertension mainly include angiotensin-converting enzyme inhibitors, angiotensin II (Ang II) receptor antagonists, calcium channel blockers, β -blockers, diuretics, and so on. For patients with poor blood pressure control, it is often necessary to take a combination of multiple antihypertension drugs (1). Despite the continuous development of antihypertension

drugs and occurrence of new surgical methods, the control of hypertension is still far from satisfactory (4). How to increase the efficiency of antiprevention drugs and delay the occurrence of hypertension-related cardiovascular diseases is a major challenge at present and even in the future.

Generally, hypertension is the result of superposition of many factors, comprising both genetic and environmental factors (5). The classic pathogenesis of hypertension involves hyperactivity of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system, vascular endothelial dysfunction, insulin resistance, dysregulation of neurohumoral factors (6,7). Recent investigations have evoked that the gut microbiota is an essential bridge between various environmental factors and our eukaryotic body, playing key roles in the development and progress of multiple diseases (8–10) and mediating the *in vivo* effects of various medicines (11–14). Previous studies on hypertension mainly focus on peripheral vascular remodeling and

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central regulation of the body, while environmental factors, especially the internal ecosystem of the human body – gut microbiota, have not been paid enough attention. Increasing studies have demonstrated that the imbalance of gut microbiota plays a key role in the occurrence and development of hypertension (15), and hypertension can also significantly impact the structure and composition of gut microbiota (16,17). Medical interventions by fecal microbiota transplantation (FMT) or supplement of specific gut microbes can effectively change animal's blood pressure (18,19). Maintaining the homeostasis of gut microbiota contributes to the satisfactory management of blood pressure. Taking gut microbiota as the starting point, this paper reviews the relationship between gut microbiota and hypertension as well as the mechanisms through which gut microbiota regulates the development and progress of hypertension, so as to provide new insights for the development of antihypertension drugs.

Research history for the relationship between gut microbiota and hypertension

The research history of for the relationship between gut microbiota and hypertension is shown in Figure 1. In 2013, a meta-analysis of 14 randomized controlled clinical trials involving 702 hypertensive patients showed that probiotic fermented milk could significantly reduce the systolic and diastolic blood pressure in hypertensive patients (20). Afterward, Yang et al. (21) reported that in spontaneously hypertensive rats (SHR) and in rats with the long-term injection of Ang II, the richness, diversity, and evenness of gut microbiota decreased significantly and the ratio of *Firmicutes/Bacteroidetes* (F/B) increased, revealing the imbalance of gut microbiota in hypertensive animals. In 2017, Li et al. (15) reported that the

richness, diversity, and gene number of gut microbiota in patients with prehypertension and hypertension were also lower than those in healthy subjects. Further investigations displayed that high-salt diet-induced hypertension involved in dysregulation of gut microbiota. Mell et al. (22) first demonstrated that high salt diet increased blood pressure through modulation of gut microbiota. Wilck et al. (19) found that a high-salt diet could significantly reduce intestinal *Lactobacillus* while supplementation of *Lactobacillus* could reduce blood pressure in salt-sensitive hypertensive mice, suggesting that *Lactobacillus* is closely related to the hypertension caused by a high-salt diet. Bartolomaeus et al. (23) found that exogenous supplementation of gut microbial metabolite propionate could decrease blood pressure in hypertensive mice induced by Ang II infusion. In 2019, Sun et al. (24) published the first population-based cohort study on the relationship between gut microbiota and hypertension, and found that the diversity of gut microbiota was negatively correlated with hypertension. There were significant differences in the structure and composition of gut microbiota in hypertensive patients with different cardiovascular risk stratifications, and some gut microbes were tightly related to the severity of hypertension (25), and suggesting that gut microbiota may participate in the process of hypertension (26). These studies suggest that gut microbiota is a key factor involved in the development and progress of hypertension.

Association of gut microbiota and hypertension

The changes of gut microbiota in hypertensive patients

In 2017, Li et al. (15) analyzed the structure of gut microbiota in healthy people, prehypertensive and essential hypertension patients through metagenomics and metabonomics. The results showed that the richness, diversity, and gene number of gut microbiota in patients with hypertension were lower than those in healthy controls, and the gut microbiota in subjects with

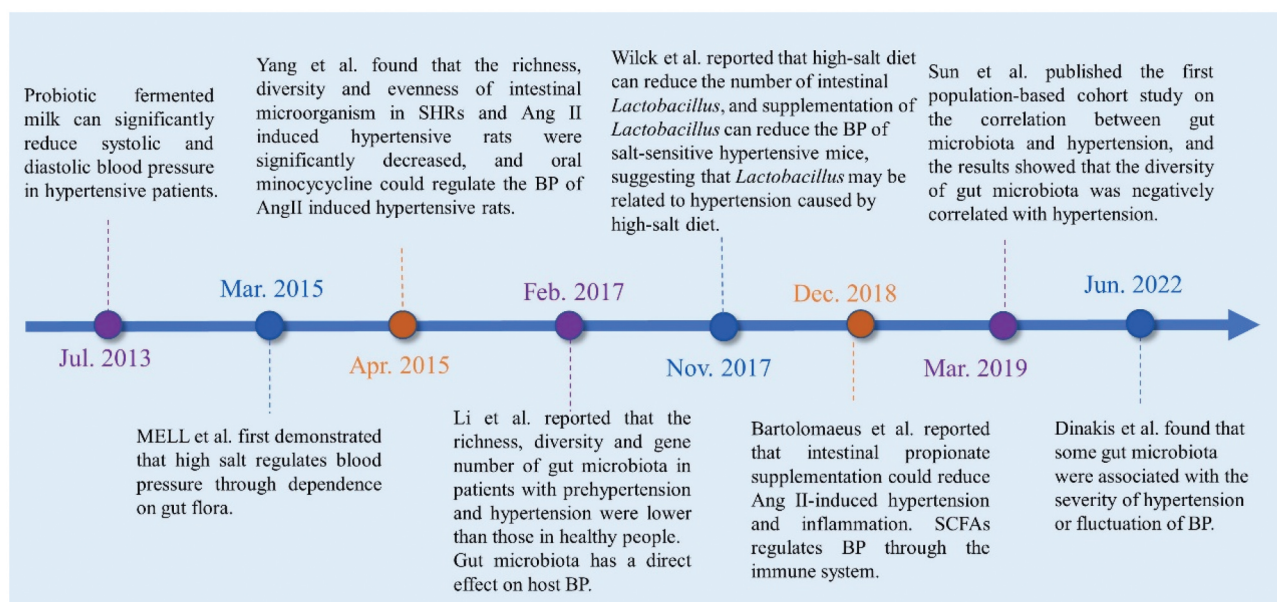


Figure 1. Research history of gut microbiota and hypertension.

prehypertension was similar to that in hypertensive patients. Later, Sun et al. (24) investigated the cross-sectional association between gut microbiota and blood pressure in the cohort of Coronary Artery Risk Development in Young Adults (CARDIA) study. They found that the gut microbial diversity was negatively correlated with hypertension. This is the first population-based cohort study on the relationship between gut microbiota and hypertension. Afterward, Liu et al. (27) used reverse transcription-quantitative polymerase chain reaction to detect the quantities of gut microbes, which showed that the number of *Bacteroides thetaiotaomicron* and *Bifidobacterium* decreased while the abundance of *Eubacterium rectale* increased in patients with hypertension. Palmu et al. (28) investigated the linkage between the gut microbiota and hypertension in a cohort of 6953 Finns study participants, which showed that hypertensive patients displayed significantly changed gut microbial genera, especially those belonging to Firmicutes. Yan et al. (17) found that some opportunistic pathogens were higher in hypertensive patients, such as, *Klebsiella*, *Streptococcus* and *Parabacteroides*, while short-chain fatty acids (SCFAs) producers including *Roseburia* and *Bacillus freundii* were higher in the control group. In a metagenomics study, the composition and function of microbiota in hypertensive patients were significantly changed and the content of fecal butyrate largely decreased compared with those from normal controls (16). Moreover, some gut bacteria are associated with the severity of hypertension and blood pressure fluctuation. The relative abundance of *Alistipes finegoldii* and *Lactobacillus* was positively correlated with lower blood pressure variability, while *Clostridium* and *Prevotella* with higher blood pressure variability (25). Another clinical study confirmed that there were significant differences in gut microbial structure and relative abundance of special taxa in hypertensive patients with different cardiovascular risk stratifications. The abundance of probiotics decreased significantly with the increase of cardiovascular risk, which suggested that gut microorganisms may be involved in the process of hypertension (26).

Changes of gut microbiota in hypertensive animal models

There are many animal models of hypertension, including spontaneous hypertension rat (SHR), Dahl salt-sensitive (DSS) rats, chronic Ang II infusion-induced hypertensive rats, stress hypertensive rats, and deoxycorticosterone acetate (DOCA)-induced sodium appetite mice. Analysis of fecal samples from SHR or chronic Ang II infusion-induced rats showed that both groups possessed similar dysbiosis of gut microbiota, that is, the ratio of F/B increased, the richness, diversity, and uniformity of microorganisms decreased, and the abundance of acetate- and butyrate-producing bacteria decreased significantly (21). Comparison between the salt-sensitive and salt-tolerant rats showed that their gut microbiota was different, especially, the number of harmful bacteria in the salt-sensitive group increased significantly (19). Wu et al. (29) found that the richness and diversity of gut microbiota in stress hypertensive rats significantly decreased. Chronic stress resulted in the increase of blood pressure in normal rats but did not in antibiotics-treated rats, indicating that gut microbiota might play an important role

in the occurrence of stress hypertension. Marque et al. (30) fed high fiber diet and acetate diet to DOCA hypertensive mice respectively. Their results showed that a high-fiber diet could reduce blood pressure by increasing the level of intestinal *Bacteroides* and acetate concentration. In addition, in the rat model of apnea syndrome with hypertension, the number of lactic acid-producing bacteria increased, while the number of *Eubacterium* that could convert lactic acid to butyrate decreased exponentially (31). Li et al. (15) transplanted feces from hypertensive patients to aseptic mice and found that systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure of the recipient mice were significantly higher than the healthy control, indicating that gut microbiota can not only regulate blood pressure in the host but also play a role in “hypertensive transmission.”

The relationship between gut barrier dysfunction and hypertension

Gut barrier dysfunction refers to the abnormal change of intestinal permeability and structural damage of intestinal mucosa caused by various reasons, which results in the translocation of bacteria and toxic products into the blood circulation and causes systemic inflammation (32). Several studies have shown that there are obvious gut microbiota disorder and gut barrier dysfunction in patients with hypertension (21,33,34). Gut barrier damage not only causes dysbiosis of gut microbiota, but also leads to an increase in intestinal permeability. Bacterial translocation caused by impaired gut barrier function results in systemic inflammation, which further leads to endothelial cell dysfunction and vascular sclerosis and eventually aggravates hypertension (35). It has been demonstrated that the incidence of gut barrier dysfunction was higher in patients with hypertension than in those without hypertension, and gut barrier dysfunction was mainly manifested by small intestinal mucosal damage and bacterial endotoxin translocation (36). Manner et al. surveyed patients with human immunodeficiency virus infection and found that endotoxin translocation caused by gut barrier dysfunction is a risk factor for hypertension, suggesting that gut barrier damage may be associated with the development of hypertension (37). Kim et al. (16) showed that intestinal fatty acid binding proteins, lipopolysaccharide (LPS), and intestinal-targeted pro-inflammatory T helper 17 (Th17) cells were significantly increased in patients with hypertension, indicating increased intestinal inflammation and permeability in hypertensive patients. Simultaneously, the levels of tight junction protein modulators in the intestinal epithelium were significantly increased, further supporting the speculation that hypertension is accompanied by gut barrier dysfunction. Furthermore, several researches discovered that SHR showed decreased intestinal mucosal thickness and blood flow, lessened glandular goblet cells, reduced intestinal villus height, decreased tight junction proteins, and increased intestinal permeability, implying that hypertension could lead to impaired intestinal barrier function (33,38).

Imbalance of gut microbiota aggravates hypertension

Gut microbiota imbalance refers to the decrease of gut microbiota diversity and the reduction of dominant genera and their beneficial metabolites, which deteriorates gut barrier function, host immune function and gut colonization resistance (39). The normal composition of gut microbiota is essential to maintain the health of the body, and the imbalance of gut microbiota is closely related to the occurrence and progress of hypertension. The ratio of F/B is an important parameter to reflect the imbalance of gut microbiota. The state of intestinal flora imbalance, especially F/B, is related to the change in blood pressure. Studies have found that F/B is significantly increased in hypertensive rat models (40), and the number of Gram-negative bacteria that destroyed the intestinal mucosal barrier increased in hypertensive patients, while the number of *Bifidobacterium* that protects the intestinal mucosal barrier decreased, which collectively aggravated the chronic inflammatory reaction (19). Robles-Vera et al. (41) found that the number of inflammatory cells in the serum and intestinal tissue of hypertensive patients increased significantly, while the number of *Bifidobacterium* decreased. *Bifidobacterium* is a probiotic and participates in the regulation of body immunity. Yan et al. (42) found that the

average levels of serum C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) in hypertensive elder patients were significantly higher than the healthy elder controls. Furthermore, they found that *Bifidobacterium* and *Lactobacillus* were negatively correlated with CRP, IL-6, and TNF- α , while *Escherichia coli* and *Enterococcus* were positively correlated with these inflammatory cytokines. Wilck et al. (19) found that *Lactobacillus* decreased in the intestines of mice fed with a high-salt diet, which may lead to the increase of Th17 cells and deterioration of salt-sensitive hypertension via driving autoimmunity. In addition, gut microbiota imbalance can destroy intestinal barrier function, increase intestinal mucosal permeability, stimulate bacterial translocation, increase serum level of endotoxin, and cause an inflammatory reaction, which ultimately leads to endothelial dysfunction and hypertension (35). Li et al. (15) transplanted fecal samples from hypertensive patients to germ-free mice and found that hypertension could be transmitted by gut microbiota, confirming that gut microbiota is an important pathogenic factor of hypertension. Both gut microbiota balance and gut barrier dysfunction play an important role in the development of hypertension. Controlling

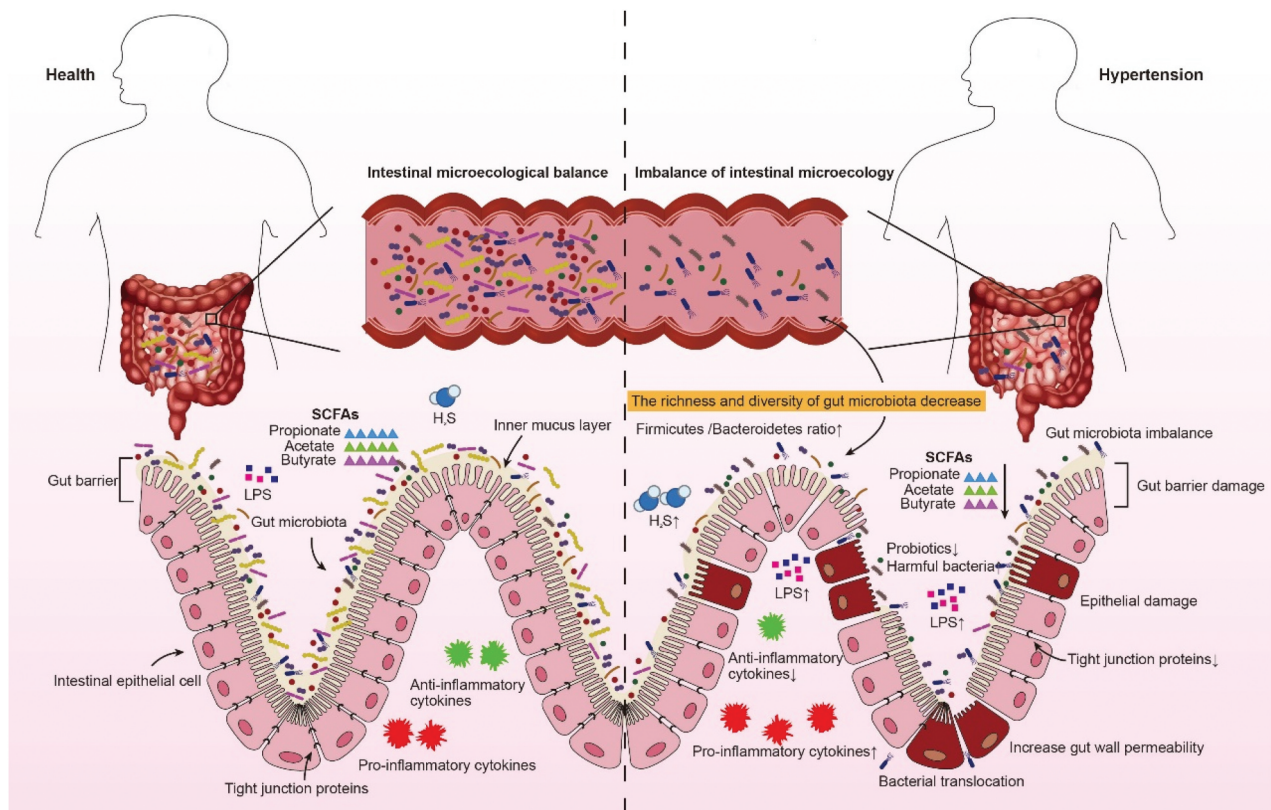


Figure 2. The relationship between gut microbiota and hypertension. In healthy individuals, the gut microbiota is in a dynamic balance, including homeostasis of gut microbiota and normal gut barrier function. Patients with hypertension have obvious gut microbiota imbalance and gut barrier dysfunction, including increased harmful bacteria and hydrogen sulfide and LPS, decreased beneficial bacteria and short-chain fatty acids, decreased intestinal tight junction proteins and increased intestinal permeability.

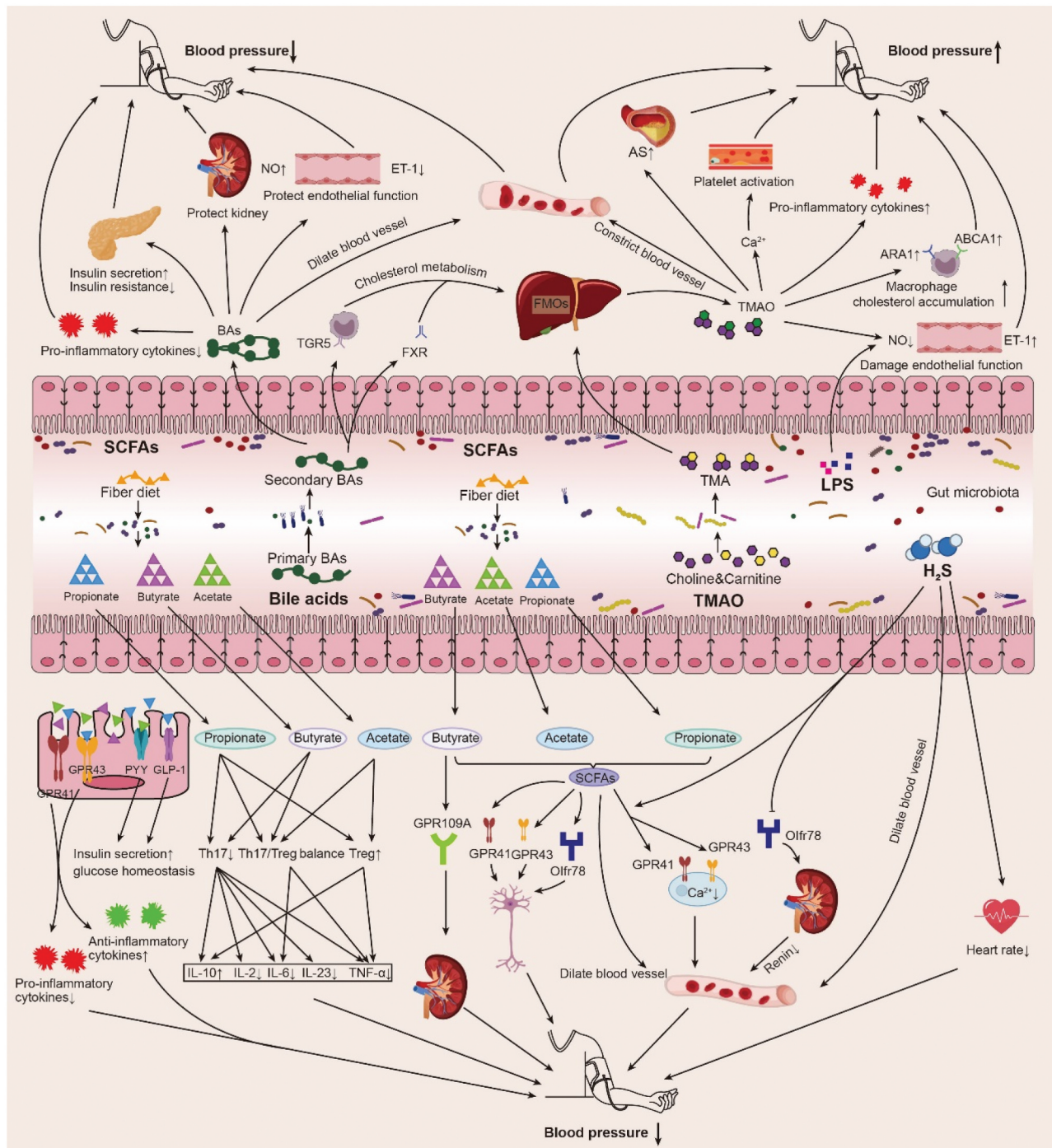


Figure 3. Relevant mechanisms of gut microbiota to regulate blood pressure. The gut microbiota can regulate blood pressure through multiple pathways. When the gut barrier function is normal, the permeability of the intestine is low, which can effectively inhibit the leakage of intestinal pathogens and enterotoxins into the body and reduce the inflammatory damage to intestinal blood vessels, thereby maintaining normal blood pressure. When the gut barrier function is impaired, intestinal permeability increases and harmful gut microbial metabolites pass through the gut barrier and enter the blood circulation to increase blood pressure. When the gut microbiota is imbalanced, a variety of pro-inflammatory factors will be over-produced, which will lead to an increase in intestinal permeability and damage the gut barrier function. At the same time, the level of enteric pathogenic bacteria and enterotoxin LPS increases, both of which will enter the blood circulation, trigger a chronic inflammatory response and damage to vascular endothelial function, thus promoting hypertension via reducing vasodilator factors and enhancing vasoconstrictor factors. Some metabolites of gut microbiota (SCFAs, BAs, H_2S) can decrease blood pressure by dilating peripheral blood vessels, maintaining vascular endothelial function, improving insulin sensitivity, lowering blood lipids, reducing inflammatory response, decreasing heart rate, inhibiting the sympathetic nervous system, and protecting kidney function, while other metabolites (TMAO, LPS) can increase blood pressure by constricting blood vessels, increasing inflammatory response, damaging vascular endothelial function, and exacerbating AS.

blood pressure by maintenance of gut microbiota homeostasis provides a novel way to prevent and treat

hypertension. The relationship between gut microbiota and hypertension is shown in Figure 2.

The mechanism of gut microbiota to regulate blood pressure

Gut microbiota participates in the occurrence and development of hypertension in various ways. Existing evidence has proven that gut barrier function, gut microbiota structure, and gut microbial metabolites are key factors involved in the occurrence and development of hypertension, [Figure 3](#).

Gut barrier function and the regulation of blood pressure

The gut barrier plays a key role in the interaction between the host and the external environment. When the gut barrier function is normal, the intestinal permeability is low, which can effectively inhibit the leakage of intestinal pathogens, enteroendotoxins, and other substances into the body, thus reducing acute and chronic inflammation in all organs ([43,44](#)), and to some extent reducing the inflammatory damage to blood vessels and lowering blood pressure. The imbalance of gut microbiota may lead to gut barrier dysfunction and increase intestinal permeability, which stimulates intestinal pathogenic bacteria and LPS entering the blood stream and results in systemic inflammation. These changes will further lead to endothelial cell dysfunction and vascular sclerosis, thus causing or aggravating hypertension ([35](#)). In addition, gut barrier dysfunction may affect the growth of probiotics, resulting in the imbalance of gut microbiota and increasing intestinal pathogenic bacteria and LPS ([45](#)). These harmful substances will enter the blood circulation through the mesentery, which further aggravates hypertension.

Gut microbiota structure and the regulation of blood pressure

Gut microbiota plays an important role in maintaining the stability of blood pressure, and the structural changes in gut microbiota is closely related to the occurrence of hypertension ([46](#)). Previous studies have shown that the structure of gut microbiota is imbalanced, and the number of harmful bacteria Proteobacteria significantly increased in hypertensive patients, which are closely related to intestinal inflammation and immune disorders ([33,47](#)). The mechanisms of gut microbiota imbalance to elicit hypertension involve several aspects. First, the imbalanced gut microbiota is usually manifested by reduced probiotics and increased harmful bacteria, which promotes inflammation and leads to abnormal expression of tight junction proteins, zonula occludin-1 (ZO-1) and occluding, in the intestinal mucosa, thus increasing the intestinal permeability and impairing gut barrier function ([48](#)). At the same time, the level of intestinal pathogenic bacteria and enterotoxin increases, and these substances enter the blood circulation through the mesentery, thus triggering a chronic inflammation and vascular endothelial damage, and resulting in decreased vasodilator factors and increased vasoconstrictor factors. The increased peripheral resistance eventually leads to increased blood pressure ([49](#)). Second, gut microbiota can regulate blood pressure through the inflammatory response. Animal experiments showed that a high-salt diet could result in a significant reduction in intestinal lactic acid

bacteria and an increase in CD4+, IL-17A+, and Th17 cells in the intestinal immune system, which caused salt-sensitive hypertension as in humans ([19](#)). Transplantation of feces from conventional high-salt-fed mice to germ-free mice elicited obvious inflammation and increased blood pressure, suggesting that gut microbiota is involved in the formation of inflammation and hypertension ([50](#)). Furthermore, gut microbiota can stimulate intestinal chromaffin cells to produce serotonin, dopamine, and norepinephrine, which also affects blood pressure levels ([49,51](#)). Additionally, gut microbiota can also regulate blood pressure by modulation of steroid hormone levels ([52](#)).

Gut microbial metabolites and the regulation of blood pressure

The gut microbiota produces many metabolites, such as trimethylamine-N-oxide (TMAO), SCFAs, corticosterone, hydrogen sulfide (H₂S), choline, bile acids (BAs), indole sulfate, LPS, etc., among which SCFAs, TMAO, BAs, H₂S, and LPS are closely related to the development of hypertension.

The mechanisms of SCFAs to regulate blood pressure

SCFAs, mainly comprised of butyrate, acetate, and propionate, are an important class of gut microbial metabolites, which are mainly produced by colonic bacteria through fermenting indigestible polysaccharides (fibers). Clinical investigations have shown that although the fecal levels of SCFAs in hypertensive people are significantly higher than that in normal controls ([53](#)), the serum levels of SCFAs are negatively correlated with blood pressure ([54](#)). Researches have demonstrated that SCFAs can directly dilate blood vessels to decrease blood pressure. In vitro experiments showed that propionate could dilate human colonic resistance arteries ([55](#)). Injection of 10 mmol/L propionates into the tail vein of wild mice can reduce blood pressure by about 20 mmHg within 1–2 minutes and the effect is dose-dependent ([56](#)). In vivo experiments have shown that supplementing butyrate or acetate in drinking water could prevent the increase of blood pressure in SHR ([57](#)), and exogenous propionate supplementation could effectively prevent hypertension in Ang II-induced hypertensive rats ([23](#)).

Investigations have shown that SCFAs can regulate blood pressure via activation of G protein-coupled receptors (GPCRs). SCFAs can interact with at least four GPCRs to regulate blood pressure ([58](#)), including G protein-coupled receptor 41 (GPR41), G protein-coupled receptor 43 (GPR43), G protein-coupled receptor 109A (GPR109A) and olfactory receptor 78 (Olfr78). Animal experiments showed that exogenous propionate supplementation effectively reduced blood pressure in Ang II-induced hypertensive rats, and this effect was related to the activation of GPR41 in the vascular endothelium by propionate ([23](#)). GPR41 and GPR43 are receptors of SCFAs, and propionate is the most potent agonist. Their interaction promoted the release of intracellular Ca²⁺ ([59](#)) and thereby reduced blood pressure. Butyrate is another key SCFA with antihypertension activity. Treatment with butyrate effectively improves proteinuria and lowers blood pressure by protecting podocytes on the glomerular basement membrane and reducing glomerular sclerosis and tissue inflammation, and this effect depends on the expression

of GPR109A level (60). Kaye et al showed that lack of prebiotic fiber predisposed mice to hypertension in the presence of a mild hypertensive stimulus, while reintroduction of SCFAs to fiber-depleted mice had protective effects on the development of hypertension, cardiac hypertrophy, and fibrosis via the cognate SCFA receptors GPR43/GPR109A (61). Another study has shown that propionate can regulate the secretion level of renin in the blood and modulate blood pressure through Olfr78 (62). In addition, SCFAs receptors Olfr78, GPR43, and GPR41 were also found to be present in the sympathetic ganglia. SCFAs can directly modulate the sympathetic nervous system by acting on receptors expressed on the sympathetic ganglia (63) and affects the neurofeedback of the gut through receptors expressed on the vagus nerve, thereby participating in the neuromodulation mechanism of blood pressure (51). Together, SCFAs, a key class of gut microbial metabolites, can regulate blood pressure by activating special GPCRs.

Modulation of immune-inflammatory response is another route through which SCFAs regulate blood pressure. Animal experiments have shown that SCFAs promote GPR43-mediated IL-10 increase, thereby reducing intestinal inflammation (64). Supplementation of SCFAs can also regulate blood pressure through modulation of Th17, regulatory T cells (Treg), etc. In AngII-induced hypertension rats, exogenous propionate exerts antihypertensive, anti-inflammatory, and anti-arteriosclerotic effects, which may be related to the immune-inflammatory response mediated by Th17, Treg, and IL-10. Depletion of intrasplenic Tregs by intraperitoneal injection of antibodies substantially abolished the cardioprotective effect of propionate, indicating a critical role of Tregs in propionate-elicited antihypertensive effect (23). Robles-Vera et al (57) administrated SHR with probiotics *Bifidobacterium breve* and *Lactobacillus fermentum* and gut microbial metabolites butyrate and acetate. They found that *Bifidobacterium breve* and *Lactobacillus fermentum* reduced blood pressure via promoting butyrate-producing bacteria, and the hypotensive effects of butyrate and acetate might be achieved by restoring the balance of Th17/Treg in mesenteric lymph nodes and normalizing endotoxin (57). Supplementation with SCFAs-producing *Lactobacillus fermentum* could reduce serum Th17 and blood pressure in both high-salt-fed mice and humans (19). Compared with healthy pregnant women, the serum levels of Th1 and Th17 were significantly increased while Treg was decreased in pregnant women with eclampsia, which was accompanied by abnormal levels of inflammatory mediators IL-8, TNF- α , and IL-17 (65). Transplantation of fecal microbes from pregnant women with preeclampsia to pre-pregnancy mice led to Th17/Treg imbalance and increased inflammatory factors in pregnant mice, which in turn elevated blood pressure (66). Exogenous supplementation of SCFAs can alleviate Th17/Treg-mediated inflammatory responses (67,68). Together, the immune-inflammatory response plays an important role in the occurrence and development of hypertension, and SCFAs can regulate blood pressure BP by modulating the levels of immune cells and inflammatory factors.

The mechanisms of TMAO to regulate blood pressure

TMAO is a gut microbial metabolite of dietary substance containing choline or trimethylamine (trimethylamine, TMA), such as phosphatidylcholine, betaine, L-carnitine, trimethylglycine, etc. The TMA lyase (such as choline TMA lyase CutC/D, betaine reductase grade, L carnitine monooxygenase CntA/B and yeaW/X) contained in specific gut microorganisms can convert above components into TMA, which is then absorbed by the host and transformed into TMAO by flavin monooxygenase 3 (FMO₃) in the liver (69,70). TMAO enters the systemic circulation and affects hypertension by altering lipid metabolism, platelet activity, obesity status, and the development of atherosclerosis (AS) (71). A meta-analysis showed that plasma TMAO levels were associated with the prevalence of hypertension in a dose-dependent manner (72). The specific mechanism of TMAO to raise blood pressure has not yet been fully elucidated. Studies have shown that TMAO enhances angiotensin II-induced vasoconstriction and promotes angiotensin II-induced hypertension, which is related to protein kinase R (PKR)-like endoplasmic reticulum kinase, PERK)]/reactive oxygen species (ROS)/Ca²⁺/calmodulin-dependent protein kinase II (CaMKII)/phospholipase C β 3 (PLC β 3) axis (73). Besides, elevated TMAO can stimulate the release of vasopressin (AVP), up-regulate the expression of aquaporin-2 (AQP-2) in the apical membrane of chief cells of the renal collecting duct, and increase sodium-water retention. In other words, TMAO can increase blood pressure through the "TMAO-AVP-AQP-2 axis" (74). Other studies have shown that TMAO can also increase blood pressure through inducing vascular endothelial dysfunction, which is achieved by promoting oxidative stress and the production of inflammatory mediators in vascular endothelial cells, and inhibiting nitric oxide (NO) synthase-induced NO production (75). However, the specific mechanism of TMAO to increase blood pressure needs more investigations in the future.

The mechanism of BAs to regulate blood pressure

BAs are the main components of bile, and their synthesis and metabolism involve the participation of gut microbes (76). As endocrine-like signaling molecules, BAs regulate lipid metabolism, accelerate energy consumption, maintain gut microbiota homeostasis and protect the intestinal barrier, thus inhibiting inflammation and preventing arteriosclerosis (AS) (77). Under imbalanced gut microbiota conditions, various pathological factors impact the homeostasis of BAs, thereby leading to the occurrence and development of multiple diseases including hypertension. BAs may affect the occurrence and development of hypertension through cardiovascular, renal and TMAO mechanisms.

The most important feature of endothelial dysfunction is the impair of vasomotor regulation. BA receptors such as nuclear receptor farnesoid X receptor (FXR) and membrane receptor G protein-coupled bile acid receptor-1 (GPBAR1) play important roles in regulating endothelial function (78,79). As endogenous vasodilators, BAs promote the production of NO and inhibit the release of Endothelin-1 (ET-1), thus regulating vasomotion and blood pressure (80). Renal-humor feedback is the main mechanism of long-

term regulation of blood pressure. Abnormal renal function is a key factor in the pathogenesis of hypertension. In mice, deletion of FXR- or TGR5-related genes is associated with reduced expression of AQP-2 and impaired urine concentration (81), which impacts the development of hypertension. FXR and TGR5 are endogenous renal receptors. BAs can regulate renal pathophysiology by activating FXR, TGR5, and genes involved in inflammation and renal fibrosis (82). Furthermore, BA metabolism is closely related to the TMAO pathway. FXR regulates the activity of FMO₃ (83). After entering the liver through the portal circulation, TMA will be oxidized into TMAO by liver FMO₃. Afterward, TMAO enters the systemic circulation and promotes hypertension by altering lipid metabolism, platelet activity, and vascular promotion of AS (71). BAs can regulate lipid metabolism by activating FXR (84). Activation of TGR5 can reduce inflammation (85), promote insulin secretion, and improve insulin resistance, which in turn regulates the occurrence of hypertension (86).

The mechanism of H₂S to regulate blood pressure

Like mammalian cells and tissues, gut microbes also produce H₂S gas which participates in multiple physiological processes,

including smooth muscle relaxation, oxidative regulation, and inflammation. H₂S is an endogenous vasoactive factor that causes concentration-dependent vasodilation. Studies have shown that Olfr78 expression is up-regulated and GPR41 and GPR43 levels are down-regulated in Ang II-induced hypertensive mice, and exogenous H₂S supplementation can partially normalize this change (87). Tomasova et al. (88) found that increasing H₂S in the gut can reduce blood pressure, while reduced H₂S production showed adverse effects on blood pressure. In addition, H₂S can decrease blood pressure by reducing the synthesis and release of renin (89,90). H₂S may also lower blood pressure by dilating peripheral blood vessels and lowering heart rate (91). However, Huc et al found that the colon-derived H₂S decreased arterial blood pressure but increased portal blood pressure (89,90). Therefore, the precise effect of H₂S on blood pressure may be site-specific.

The mechanism of LPS to regulate blood pressure

Gut microbiota disturbance can cause increased secretion and release of intestinal LPS into the blood circulation, which then activates intestinal inflammatory response, damages intestinal mucosal function, and increases intestinal permeability. LPS is a component of Gram-negative bacteria such as *Escherichia*

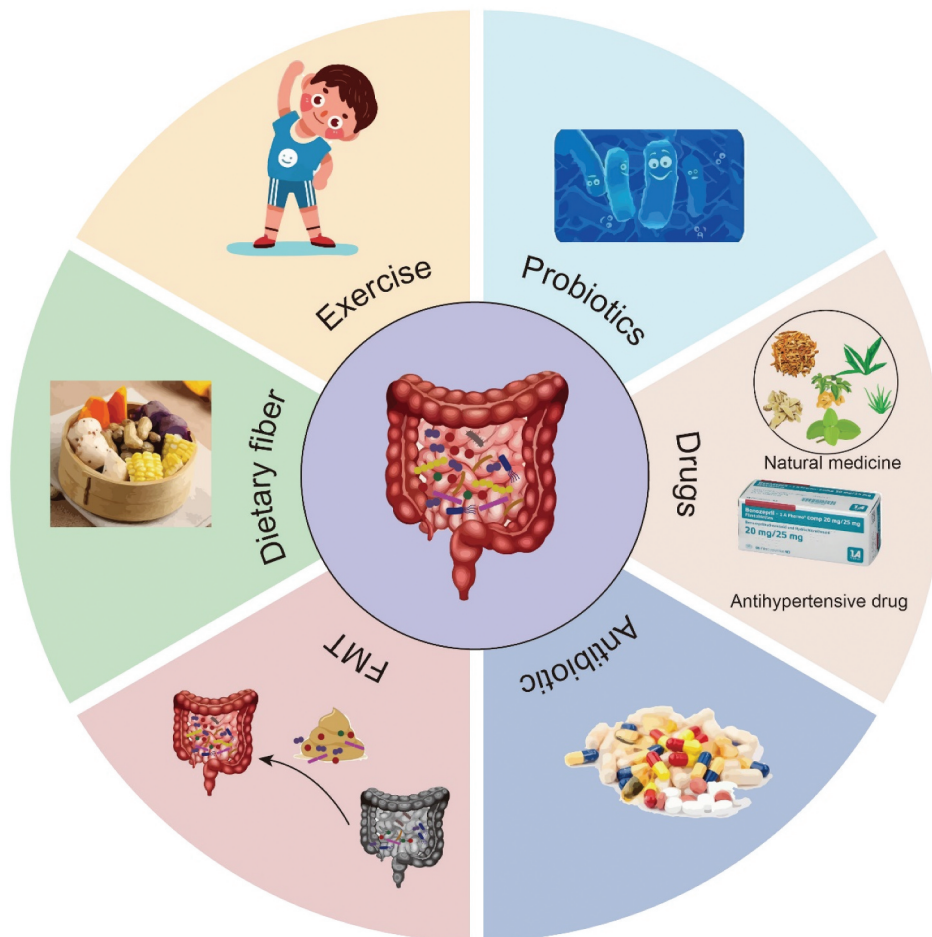


Figure 4. Interventions to regulate gut microbiota.

coli. In animal experiments, LPS can be used to induce vascular dysfunction (92). The integrity of the intestinal barrier and the expression of tight junction proteins in hypertensive patients are damaged, which promotes LPS entering blood circulation to trigger inflammatory response and aggravate hypertension (16,93). Supplementation of probiotics can effectively ameliorate vasodilation, vascular inflammation and hypertension, and these effects were accompanied by decreased LPS levels (94).

Management of hypertension by regulation of gut microbiota

Gut microbiota is closely related to the occurrence and development of hypertension. Therefore, exploring gut microbiota-based intervention methods may provide new strategies for the treatment of hypertension. At present, the main methods to regulate the gut microbiota include FMT, supplementation of probiotics, antibiotics, diet and exercise, antihypertensive drugs, and natural medicines (Figure 4).

FMT

FMT refers to the transplantation of functional bacteria from the stool of a healthy host into the gastrointestinal tract of the patient to rebuild the gut microbiota and achieve the therapeutic purpose. In recent years, more and more attention has been paid to the therapeutic effect of FMT on hypertension. Studies have shown that transplanting feces from hypertensive rats into healthy rats resulted in typical hypertension, while transplanting feces from healthy rats into hypertensive rats can reduce blood pressure (95). Kim et al. (96) transplanted fecal bacteria from healthy mice fed with resveratrol into Ang II induced hypertensive mice and found that the systolic blood pressure (SBP) of hypertensive mice was reduced, which indicated that FMT may be a way to treat hypertension. At present, the mechanism of FMT to alleviate hypertension is still unclear. High-quality clinical trials are still needed to provide rigorous evidence for the effectiveness of FMT to treat hypertension.

Probiotics

Probiotics can change the diversity and structure of gut microbiota, regulate the production of gut microbial metabolites, and improve blood pressure. Clinical trials have found that supplementation of probiotics effectively reduces blood pressure in hypertensive patients. Khalesi et al. (97) conducted a systematic review on the effectiveness of probiotics to control blood pressure. Compared with the control group, intake of probiotics significantly reduced systolic and diastolic blood pressure, and probiotics combination showed more obvious antihypertensive effects than a single one. A meta-analysis based on 14 randomized placebo-controlled clinical trials showed that hypertensive patients received probiotic fermented milk showed a mean decrease in SBP of 3.10 mmHg and DBP of 1.09 mmHg, suggesting that probiotics can effectively reduce systolic and diastolic blood pressure (20). A study in elderly people showed that consumption of dairy products

containing *Lactobacillus casei* fermentation at least 3 times per week can reduce the risk of hypertension (98). In addition, *Lactobacillus* and *Bifidobacterium* can exert antihypertensive effects via regulating the renin-angiotensin system (RAS) by producing angiotensin-converting enzyme (ACE) inhibitory peptides, SCFAs, conjugated linoleic acid and gamma-aminobutyric acid (GABA) (99,100). Sipola et al. (101) reported that yogurt fermented by *Lactobacillus* LBK-16 H contained ACE inhibitory peptides which could effectively delay the progression of hypertension in SHR. Mizushima et al. (102) showed that daily intake of 160 g of *Lactobacillus*-fermented yogurt for 4 weeks resulted in a decrease in SBP of 5.2 mmHg and DBP of 2.0 mmHg. Inoue et al. (103) reported that ingest of *Lactobacillus*-fermented yogurt for 12 weeks decreased SBP by (17.4 ± 4.3) mmHg and decreased DBP by (7.5 ± 5.7) mmHg in patients with mild hypertension. Overall, probiotics is promising to treat hypertension, but more studies are needed to fully understand their mechanisms to control blood pressure.

Antibiotics

The effectiveness of antibiotics to treat hypertension remains controversial and individual difference should be noted. Yang et al. (21) found that high blood pressure is associated with gut microbiota dysbiosis and treatment with minocycline could rebalance the dysbiotic gut microbiota and attenuate hypertension. Galla et al. (104) used amoxicillin to change the gut microbiota of young genetically hypertensive rats and pregnant and lactating rats. Amoxicillin remodeled the structure of gut microbiota and reduced the ratio of F/B, which eventually decreased blood pressure. In young rats treated with amoxicillin, the blood pressure-lowering effect persisted even after antibiotic discontinuation. These results suggest that antibiotics can decrease blood pressure through remodeling gut microbiota. In an experiment on drug interaction between amlodipine and antibiotics (ampicillin), gut microbiota participated in the metabolism of amlodipine, and the intake of antibiotics may improve the bioavailability of amlodipine by inhibiting gut microbes, thus improving its antihypertensive efficacy (105). It has been reported that the combination of antibiotics to inhibit the growth of some gut bacteria can reduce blood pressure in the treatment of refractory hypertension (106). However, some studies have revealed that the antihypertensive effects of antibiotics are not the same on different animal models. Galla et al reported that oral administration of antibiotics increased systolic blood pressure of the Dahl salt-sensitive rat, while minocycline and vancomycin, but not neomycin, lowered systolic blood pressure in the SHR (107). At present, the clinical research on the antihypertensive effect of antibiotics is relatively insufficient. The feasibility of antibiotics for the treatment of hypertension needs further investigation because of the high adverse effects of antibiotics to human beings.

Diet and exercise

There is increasing evidence that dietary nutrients are essential for the maintenance of gut microbiota homeostasis and host

health (108–110). A high-fiber diet attributes to healthy gut microbiota and exerts antihypertensive effect. Feeding with high-fiber diet to hypertensive mice effectively reduced blood pressure (30). Ingest of high-fiber diet increases the amount of acetate and other SCFAs and modulates the structure and composition of gut microbiota, which is beneficial for blood pressure control. SCFAs are usually fermentation products of indigestible polysaccharides (fiber) by gut microbes. Dietary fiber can modulate gut microbiota and promote the production of SCFAs (acetic acid, propionic acid, butyric acid, etc.). Both systolic and diastolic blood pressure of hypertensive mice can be effectively decreased by supplementing high-fiber food and acetate (56). Therefore, dietary supplementation of fiber and SCFAs can alleviate hypertension and maintain normal blood pressure. Marque et al. (30) showed that a high-fiber diet could play an antihypertensive role by increasing the level of intestinal *Bacteroides* and the concentration of acetate. Exercise can also increase the diversity of gut microbiota, promote SCFAs production, and regulate blood pressure (111). Compared with sedentary people, the levels of SCFAs in athletes are relatively increased (112). Simultaneously, exercise can increase the diversity and richness of gut bacteria, enhance the levels of SCFAs and BAs, and improve inflammatory response (112).

Drug intervention

Antihypertensive drugs

Losartan, captopril, benazepril, and amlodipine are common antihypertensive drugs. Robles-Vera et al (113) evaluated the effect of the angiotensin receptor antagonist losartan on the gut microbiota of SHR and found that losartan significantly changed the structure of gut microbiota. To some extent, losartan can protect the vascular system and reduce blood pressure by regulating the intestinal immune system. Other studies have shown that angiotensin-converting enzyme inhibitor captopril can reduce blood pressure and restore the permeability of the intestinal barrier in SHR (33). Xu et al (114) assessed the impact of benazepril and amlodipine on gut microbiota in SHR and found that both drugs modulated the α and β diversity of gut microbiota and changed the composition at the phylum and genus levels. Gut microbiota is also involved in the metabolism of amlodipine, and combination with antibiotics improves the bioavailability of amlodipine and enhances its antihypertensive effect (105).

Natural medicines

It has been shown that natural medicines can alleviate hypertension through modulation in different ways, such as regulating the ratio of probiotics to pathogenic bacteria, restoring the diversity of gut microbiota, improving intestinal barrier function, and regulating the metabolites of gut microbiota (115). Ma et al (116) showed that treatment with Huanglian Jiedu decoction for 6 weeks increased the diversity of gut microbiota, enhanced the abundance of *Lactobacillus*, and decreased Firmicutes. It is speculated that Huanglian Jiedu decoction may reduce blood pressure through regulating the structure of gut microbiota, promoting beneficial bacteria, and inhibiting harmful bacteria (117). Wu et al (118) found that

Sanhuang Xiexin decoction could dilate blood vessels, protect vascular endothelial cells, and decrease blood pressure, which is accompanied by significantly increase of beneficial bacteria such as *Lactobacillus*. Administration of *Radix Astragali-Radix Salviae Miltiorrhizae* to SHR for 28 days effectively decreased the blood pressure and enhanced the diversity of gut microbiota. The increase of probiotics such as *Lactobacillus* and *Bifidobacterium* was closely related to the decrease of blood pressure (119). Qi et al (120) assessed the effect of *Eucommia ulmoides-Tribuli Fructus* (EUTF) on blood pressure and gut microbiota in SHR. They found that EUTF could reduce blood pressure and increase the diversity of gut microbiota, suggesting that the antihypertensive effect of EUTF is associated with the improvement of gut microbiota. Xiong et al (121) found that Qinggan Yishen Qufeng could improve the intestinal permeability, increase the expression of intestinal tight junction protein, and reduce the intestinal damage caused by hypertensive lesions. Yu et al (122) showed that the antihypertensive drug Zhengan Xifeng decoction could effectively reduce the F/B value and enhance the production of SCFAs, thereby maintaining the ecological balance and integrity of the intestinal tract. It has been well-documented that some natural products such as berberine (123) and guneulsterone (124) can regulate the gut microbiota-TMA pathway to reduce the TMAO levels in peripheral blood. Resveratrol can regulate BAs and down-regulate the farnesoid X receptor -fibroblast growth factor 15 (FXR-FGF15) pathway, which plays a role in preventing atherosclerosis in ApoE^{-/-} mice (125). Quercetin can reduce the production of LPS and alleviate inflammation, thus improving vascular remodeling and lowering blood pressure (126). Han et al (127) reported that Huangqi (*Astragali Radix*) plus Danshen (*Salviae Miltiorrhizae Radix Et Rhizoma*) could improve gut microbiota and enhance the production of beneficial metabolites, thus reducing blood pressure SHR.

Conclusion and perspectives

Gut microbiota and its metabolites are closely related to the occurrence and development of hypertension. Investigating the correlation between gut microbiota and hypertension may help to reveal the pathogenesis of hypertension from the perspective of gut microbiota, which is of great significance for the prevention and treatment of hypertension. Gut microbiota-targeted antihypertensive therapy is a promising strategy, providing great inspiration for solving the dilemma of current hypertension treatment. The study on the mechanisms of gut microbiota in the formation of hypertension not only aims to explore the etiology, but also provides a large number of new targets for clinical treatment, which is helpful to develop novel drugs to treat hypertension and choose proper antihypertensive drugs based on the specific gut microbial characteristics in individuals. Treatment of hypertension by regulating gut microbiota may be a new strategy that makes up for the deficiency of current antihypertensive therapies. The combination of a high-fiber diet, probiotics and prebiotics, fecal bacteria transplantation, natural medicines, and other gut microbiota-targeted therapies with conventional drugs may be a new approach to achieve ideal hypertension management.

Due to the complex etiology of hypertension and the diverse structure of gut microbiota, the current research on the relationship between gut microbiota and hypertension is still in the initial stage, and the research methods are not mature enough. In addition, the relationship between gut microbiota and hypertension is heavily affected by diet, exercise, drugs, psychology, and other factors. Therefore, future studies should pay special attention to the standardization of sample acquisition, processing and metagenomic data analysis. The establishment of a microecological characteristic diagnosis and treatment system for hypertension based on gut microbiota can provide a constructive scheme for the prevention and treatment of hypertension in the future. According to the specific function of microorganisms, new probiotics can be developed to promote human health. Gut microbiota is directly or indirectly involved in diet and drug metabolism. Therefore, it is helpful to realize the characteristic diagnosis and treatment model of hypertension as soon as possible by studying the targeted and specialized drug delivery of gut microbiota and mining new bacteria, new genes, and new functions.

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