



The Role of Gut Microbiota in Hypertension Pathogenesis and the Efficacy of Antihypertensive Drugs

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Abstract

Purpose of Heading To review the relationship between intestinal microbes and hypertension and its impact on the efficacy of antihypertensive drugs, and help to address some of these knowledge gaps.

Recent Findings Hypertension is associated with cardiovascular diseases and is the most important modifiable risk factor for all-cause morbidity and mortality worldwide. The pathogenesis of hypertension is complex, including factors such as dietary, environmental and genetics. Recently, the studies have shown that the gut microbiota influences the occurrence and development of hypertension through a variety of ways, including affecting the production of short-chain fatty acids, dysfunction of the brain-gut axis, and changes in serotonin content that cause the imbalance of vagus and sympathetic nerve output associated with hypertension. However, patients with hypertension typically take antihypertensive drugs orally on a long-term basis, and most antihypertensive drugs are absorbed by the gastrointestinal tract. Studies have shown that the pharmacokinetics and metabolism of antihypertensive drugs may be influenced by microbiota, or antihypertensive drugs act directly on the intestinal flora to exert efficacy, including regulation of intestinal microbial metabolism, intestinal inflammation, and intestinal sympathetic nervous system disorders.

Summary The intestinal flora can affect the pharmacokinetics and metabolism of antihypertensive drugs in the rats, and intestinal microbiota also can be the target “organ” by antihypertensive drugs.

Keywords Gut microbiota · Hypertension · Antihypertensive drugs · Pharmacokinetics · Metabolites

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Introduction

Hypertension is a well-admitted risk factor for cardiovascular diseases worldwide. By the current standard of SBP/DBP > 130/80 mmHg from the 2017 American College of Cardiology (ACC)/American Heart Association (AHA) hypertension guidelines, the prevalence of hypertension is significantly increased. In the United States, the current prevalence of hypertension is estimated to be 45.6% (from 31.9%) [1]. Atasoy et al. found the current standard increased the prevalence of hypertension from 34 to 63% in the Prospective MONICA/KORA Study [2]. Researchers often tend to assume that hypertension is caused by the dual role of genetics and unhealthy lifestyle. Though the widespread use of antihypertensive drugs made the global average blood pressure degressive over the past few decades, the prevalence of hypertension is increasing due to aging population and increased risk factors exposure [3]. These risk factors include high sodium intake, low potassium intake, alcohol consumption, lack of physical activity, unhealthy diet, smoking, air pollution, psychological stress, noise exposure, and sleep-

related breathing disorders. Recent studies have also found that the prevalence of apparent treatment-resistant was 14.7% in the population of treated patients with hypertension and only a minority of patients (almost 32.5%) receiving treatment were controlled [4, 5]. It shows that the treatment of hypertension has also encountered a bottleneck and there are lots of problems that have yet to be resolved. Hypertension may be a long-term burden of the health system.

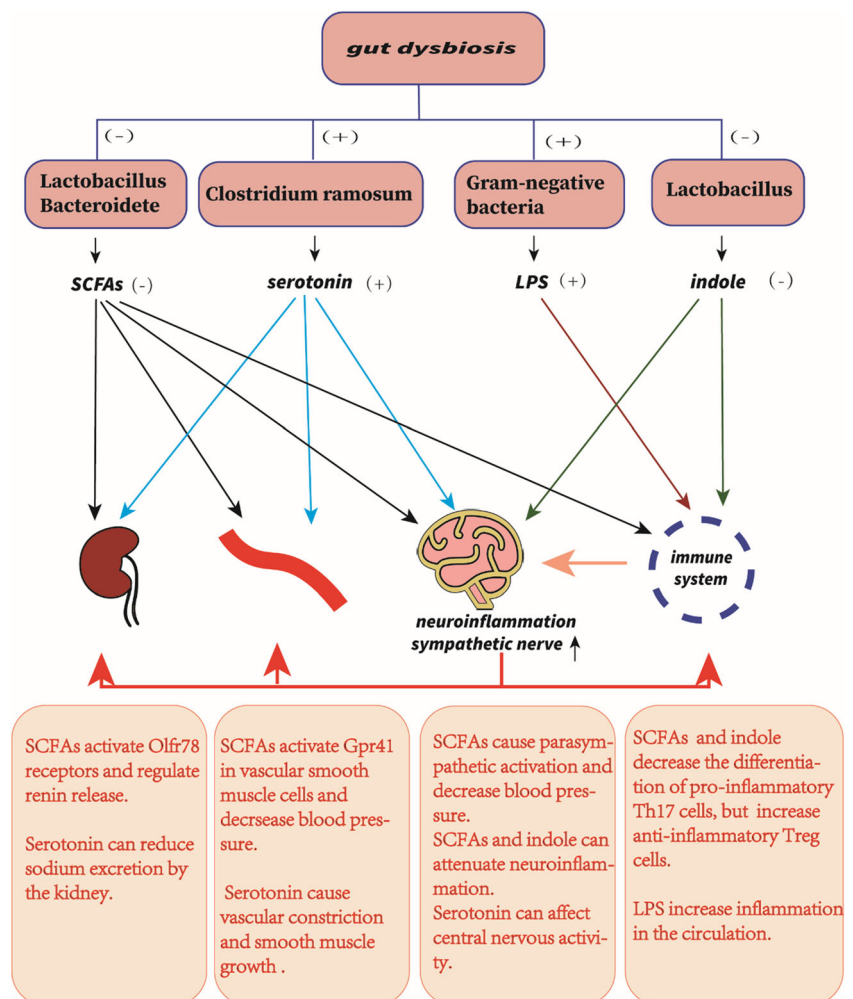
In recent years, research on the potential role of intestinal microbiota on host health has become a hot spot. Studies have found that gut dysbiosis is closely related to the occurrence of hypertension. In hypertensive patients and rats, intestinal microbiota imbalance [6, 7], microbial-derived metabolite changes [8, 9], and intestinal pathological changes have been found [10, 11]. Gut microbiota and its metabolites have a pivotal role in pathogenesis of hypertension, and the pathophysiological mechanism of gut microbes involved in hypertension is complex (Fig. 1). Studies have also found that the therapeutic effects of hypertension drugs are affected by the intestinal microbiota. Intestinal microbiota and its metabolites may influence the absorption and metabolism of

antihypertensive drugs [12], and subsequently alter the pharmacokinetics of these drugs, and intestinal microbiota also can be the target “organ” as well as the canonical antihypertension organs by antihypertensive drugs (Fig. 2). The restore of intestinal microbiota balance by antihypertension drugs has direct effect on lowering blood pressure [13, 14]. The specific mechanism behind these is not clear now; however, we will review limited studies which have been done and explore the possible mechanisms in which gut microbiome acts. Research on the intestinal microbiota and antihypertensive drugs will provide a new path for the treatment of hypertension through targeting the intestinal microbiota and provide more understanding of individual difference of antihypertensive efficacy among hypertension patients by antihypertensive drugs.

The Gut Microbiota

Gut microbiota has nearly 10 to 100 trillion bacteria, mainly settling in the colon. In the human intestine, except for

Fig. 1 The mechanism of gut dysbiosis causing increased blood pressure. In the figure, (+) and (-) are used to indicate changes in the microbiota and metabolites when gut dysbiosis happens. The directions of the arrow indicate that the metabolite has an effect on the organ or system, and the corresponding effect is described below. Finally, neuroinflammation caused by immune system leads to sympathetic nerve activation, which in turn affects the kidneys, blood vessels, and immune system.



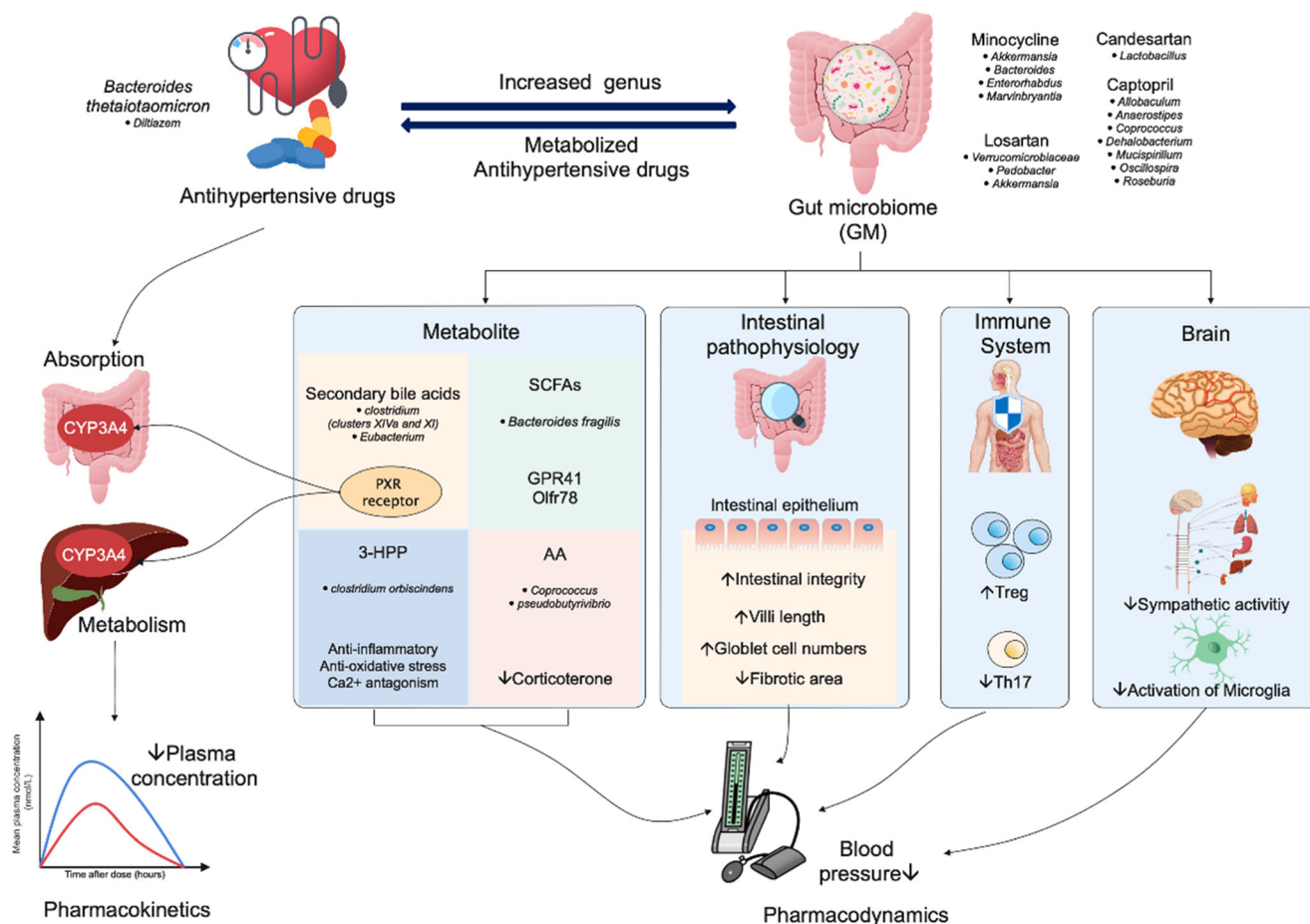


Fig. 2 The mechanism of antihypertensive drugs reducing blood pressure through gut microbiome. Antihypertensive drugs can change the number of some gut microbiota, such as losartan can increase the number of *Lactobacillus*. Some gut microbiota can directly metabolize antihypertensive drugs, such as diltiazem can be metabolized by *Bacteroides thetaiotaomicron*. Antihypertensive drugs can affect the pharmacokinetics and pharmacodynamics of the gut microbiota.

Antihypertensive drugs affect the production of secondary bile acids and activate PXR receptors, thereby affecting the pharmacokinetics of antihypertensive drugs by changing the enzyme activity of CYP3A4. Antihypertensive drugs affect the pharmacodynamics of antihypertensive drugs by affecting the metabolites of gut microbiota (such as SCFAs), intestinal pathophysiology, intestinal immunity, and brain-gut axis.

bacteria, there are viruses, fungi, bacteriophages, and archaea. At the phylum level, nearly 90% of gut bacteria belong to *Bacteroidetes*, *Firmicutes*, and *Actinobacteria*. The remaining phyla include *Verrucomicrobia*, *Fusobacteria*, and *Proteobacteria*. The composition of the microbiota is influenced by host genetic factors [15], age, geography [16], disease state [17], and the external environment factors. These environment factors refer to dietary habits (vitamin, fat, and dietary fiber) [18, 19], drug treatments [20], and intestinal motility [21]. A recent research even found that host fecal miRNA regulates gut microbiota through regulating microbial gene expression and growth [22].

The microbiota inhabiting the intestines plays important roles in host health and disease. Gut microbiota influences host numerous functions, such as nutrient absorption, metabolism [23], immune system, aging [24], nervous system, and endocrine function [25], and can regulate intestinal epithelial barrier and prevent pathogenic bacterium colonization [26].

Some common diseases also associate with gut microbiota, including allergic and immune disorders, colorectal cancer, gynecological and reproductive disorders, metabolic disorders (cardiovascular disease, kidney disease, obesity, type 2 diabetes), neurological disorders, and other gastrointestinal disorders [17, 27–29].

The connection between microbiota and host is partly through bacteria-derived metabolites and small molecule intermediates in metabolic processes, such as short-chain fatty acids (SCFAs), bile acids (BAs), lipopolysaccharide (LPS), indoles, and trimethylamine N-oxide (TMAO). It is generally believed that microbial metabolism provides energy for the host and itself. For example, colonocytes can use butyrate as an energy source by SLC5A8 pathway. Fiber that the human body cannot digest is the energy source of intestinal bacteria [30]. However, researchers found these bacteria-derived metabolites and small molecule intermediates can act as biological signal molecules to mediate the communication between

microbiota and the host and trigger a series of physiological or pathological changes. SCFAs produced by dietary fiber metabolism can maintain gut barrier [11], anticancer, influence host metabolism, and inhibit histone deacetylases [31•]. SCFAs seem to be an extremely important metabolite of intestinal microbiota in regulating blood pressure. BAs can regulate gut microbiota composition and influence host metabolism [32]. The study of intestinal microbiota and their metabolites will bring promising prospects for the diagnosis and treatment of diseases.

The Link Between the Gut Microbiome and Hypertension

Characteristic Changes of Intestinal Bacteria

The relationship between gut dysbiosis and hypertension has been explored over the past few years. Studies have found changed gut bacteria in hypertensive animals or hypertensive patients [6–8, 10, 11, 33–39]. The relevant research results are listed in Table 1. Li et al. found that in both pre-hypertension and hypertension populations, microbial richness and diversity dramatically decreased compared to the healthy controls [8••], but some bacteria such as *Prevotella* and *Klebsiella* overgrew. Yang et al. found in hypertensive animals and patients, the ratio of Firmicutes/Bacteroides increased, acetate- and butyrate-producing bacteria decreased, but lactate-producing microbial populations increased. Kim et al. found there were seven bacterial species (*Klebsiella* unclassified, *Parabacteroides johnsonii*, *Eubacterium siraeum*, *Prevotella bivia*, *Anaerotruncus* unclassified, and *Rummimococcus torques*) positively correlated with systolic blood pressure (SBP) [11]. Due to differences in animal strains or human races, the results of differences in intestinal microbiota obtained from animal experiments or human experiments are all different.

Studies have also found that by changing the intestinal microbiota, the blood pressure can be changed. Joe et al. found that the germ-free (GF) mice had a lower blood pressure compared to their conventionalized counterparts [41]. Transferring feces from patients with hypertension to GF mice can cause mice to elevate blood pressure. On the contrary, transplanting fecal matter from normotensive donor rats to hypertensive recipients significantly decreased blood pressure [9]. These evidences indicate gut microbiota and hypertension are in close contact with each other. Intestinal microbiota actively involved in the occurrence of hypertension.

Pathological Alterations in the Intestine

Research on patients and mice with hypertension found characteristic changes in intestinal structure. The permeability and

stiffness of gut barrier increased in spontaneously hypertensive rats (SHRs) and in rats with Ang-II-induced hypertension [10, 11, 42]. In addition, the levels of tight junction proteins including occludin (Ocln), tight junction protein 1 (Tjp1), zonula occludens-1 (ZO-1), and claudin 4 (Cldn4) decreased and gut fibrosis increased. There is also an increase in intestinal inflammation, showing increased macrophages, T cells, and the cytokines. The level of tyrosine hydroxylase in the small intestine increased [10••]. Sympathetic neuronal communication between the gut and the hypothalamic paraventricular nucleus enhanced. We have not got a conclusion on the precedence relationship between these pathological changes and the occurrence of hypertension so far.

Gut Microbiota Changes Short-Chain Fatty Acid Composition

SCFAs are produced by the fermentation of dietary fiber by microbiota. The most common SCFAs are acetic acid, propionic acid, and butyric acid [43]. SCFAs can regulate blood pressure, by acting on the olfactory receptor (Olf1r) 78 (OR51E2 in humans) and G protein-coupled receptor (GPR) 41. Olf1r78^{-/-} mice showed lower BP associated with lower levels of plasma renin, which indicated SCFAs-mediated renin release from the juxtaglomerular cells through Olf1r78 receptors and activation of Olf1r78 receptors may increase blood pressure [44]. Propionate can also activate GPR41 in vascular smooth muscle cells and play a hypotensive effect [45]. In GPR41 knockout mice, researchers found these mice displayed isolated systolic hypertension [46]. The activation of GPR41 and Olf1r78 by SCFAs will have an antagonistic effect and participate in the regulation of blood pressure.

In addition, SCFAs also participate in the regulation of the nervous system and immunity, indirectly regulating blood pressure. SCFAs affect the biology of immunes through GPRs expressed in these cells. SCFAs can especially inhibit the expression and function of immune cell histone deacetylase [31•]. Butyrate can also maintain the integrity of the intestinal barrier through promoting the production of GLP-2, contributing to the hypoxic environment of the lumen [11]. SCFAs may be important intermediates between the intestinal microbiota and the blood pressure. However, the research on the effect of SCFAs on human blood pressure is still very limited.

Gut Microbiota Changes the Brain–Gut–Bone Marrow Axis

Researchers have proclaimed sympathetic nervous system can be activated by neuroinflammation and some risk factors for hypertension. Neuroinflammation can induce central sympathetic nerve activation and, subsequently, cause blood pressure to rise through a series of innervations. Increased

Table 1 Upregulated or downregulated gut bacteria in hypertensive animals or hypertensive patients compared with normal controls.

Researchers	Strain/race	Research object	Research tool	Dietary habits	Upregulated	Downregulated
Yan et al. [6]	Chinese	60 patients with primary hypertension and 60 healthy controls	Whole-metagenome shotgun sequencing	-	Klebsiella, Streptococcus, Parabacteroides, Eggerthella, Salmonella	Roseburia Faecalibacterium Synergistetes
Wilck et al. [7]	FVB/N mice	High-salt diet mice ($n = 12$); normal salt diet mice ($n = 8$)	16S rRNA sequencing	Purified diets (NSD: 0.5% NaCl, HSD: 4% NaCl)	Akkermansia, Parasutterella, Clostridia, Alistipes	Lactobacillus Pseudoflavonifractor Prevotellaceae Bacteroidetes
Li et al. [8••]	Chinese	Pre-hypertensive ($n = 56$), hypertensive patients ($n = 99$), and healthy controls ($n = 41$)	Illumina sequencing	All no-antihypertensive treatment	Prevotella, Klebsiella, Enterobacter, Fusobacterium	Bacteroidetes Oscillibacter Faecalibacterium Butyrivibrio Roseburia Bifidobacterium Coprococcus
Kim et al. [11]	American	Hypertensive patients and reference subjects	Shotgun metagenomics	-	Parabacteroides johnsonii, Klebsiella, Anaerotruncus, Ruminococcus, Eubacterium siraeum, Alistipes finegoldii, Prevotella bivia	Bacteroides Paraprevotella
Marques et al. [31•]	C57Bl/6 mice	Sham ($n = 25$) or DOCA surgery ($n = 39$) mice	16S rRNA sequencing	Control diet, high-fiber diet, acetate supplementation	Cyanobacteria, Proteobacteria	Bacteroidetes Firmicutes
Yang et al. [34••]	WKY rats and SHRs	SHRs and WKY rats	16S rDNA sequencing	-	Firmicutes to Bacteroidetes ratio, lactate-producing bacteria (Streptococcus and Turicibacter)	Acetate- and butyrate--producing bacteria Actinobacteria (Bifidobacterium)
Bier et al. [35]	Dahl salt-sensitive rats	High-salt diet mice Normal salt diet mice	16S rRNA-amplicon sequencing	NSD (0.5% NaCl, 44.2% carbohydrates, 18.6% protein, 6.2% fat); HSD (4% NaCl, 46.7% carbohydrates, 18.5% protein, 5.3% fat)	Erwinia genus, Christensenellaceae, Corynebacteriaceae	Anaerostipes genus
Adnan et al. [36]	WKY rats and SHRs	SHRs and WKY rats	16S rRNA sequencing	-	Firmicutes, Lactate-producing bacteria (Lactobacillus)	Acetate- and butyrate--producing bacteria (Bacteroidetes, Clostridiaceae, Holdemania, Coprobacillus)
Callejo et al. [37]	Wistar rats	Pulmonary arterial hypertension rats and normal rats	16S rRNA sequencing	Normal rat chow	Firmicutes Actinobacteria	Proteobacteria, Bacteroidetes Verrucomicrobia
Sun et al. [38]	African- and European-American	High blood pressure groups and	16S rRNA sequencing	-	Anaerovorax, Clostridium IV, Oscillibacter, Sporobacter,	Ruminococcaceae Anaeroglobus, Atopobium, Lactobacillus,

Table 1 (continued)

Researchers	Strain/race	Research object	Research tool	Dietary habits	Upregulated	Downregulated
		normal controls			Veillonellaceae, Butyricoccus, Cellulosibacter, Papillobacter, Sporobacter, Vampirovibrio	Megasphaera, Pseudocitrobacter, Rothia
Verhaar et al. [39]	HELIUS Cohort (Dutch, South Asian, Surinamese, African, Surinamese, Ghanaian, Turk, or Moroccan)	High blood pressure groups and normal controls	16S rRNA gene amplicon sequencing	-	Streptococcus spp. Klebsiella spp. Escherichia/Shigella spp.	Roseburia spp., Clostridium sensu stricto spp., Roseburia hominis, Romboutsia spp., Ruminococcaceae NK4A214 spp., Enterorhabdus
Santisteban et al. [40]	WKY rats and SHRs	SHRs and WKY rats	Illumina Miseq 16S rDNA sequencing	Standard rat chow	Lactobacillales, Firmicutes	Bifidobacterium, Actinobacteria, Bacteroidetes

SHRs spontaneously hypertensive rat; WKY Wistar-Kyoto

sympathetic nerve activity was linked with elevated inflammation both systemically and in the gut [40, 47]. Sympathetic nerve activation leads to increased intestinal permeability, causing intestinal dysbiosis and inflammatory state.

Gut microbiota and metabolites can regulate brain inflammation and change sympathetic nerve activity. SCFAs produced by intestinal bacteria can reduce brain oxidative stress and neuroinflammation through microglia and astrocytes, and affect sympathetic activity. Yang et al. found that central administration of butyrate in the SHR reduced the activation of cardio regulatory regions [48]. GF mice showed reduced intestinal tight junction proteins and increased blood-brain barrier (BBB) permeability [49]. Butyrate supplementation can restore the tight junction protein and blood-brain barrier to normal values. But oral administration sodium butyrate was found to decrease BBB permeability [49]. The effect of SCFAs on the brain barrier still needs to be studied. Tryptophan metabolites (indole) could affect astrocytes via aryl hydrocarbon receptor signaling and attenuate neuroinflammation [50, 51]. BAs can pass through the BBB and activate GPR 1 expressed on astrocytes to reduce neuroinflammation [52]. BAs can also reduce oxidative stress in the brain through microglia.

Gut microbiota and their metabolites also play an important role in activating the immune system. Studies found that GF animals have a reduction in the levels of Th17 cells and B cells, and impaired Treg cell function [53–57]. Gut dysbiosis caused changes in microbial metabolism and then increased permeability and stiffness of the gut barrier. Studies found LPS whose synthesis and transport increased in hypertensive patients can increase inflammation in the circulation. Peripheral inflammation shows multiple types of T-cell activation and increased inflammatory cytokines, which affect vasoconstriction and renal sodium handling [58]. Eventually,

the blood pressure will rise. SCFAs have an opposite effect [33]. SCFAs may affect T-cell differentiation. Propionate decreases the differentiation of pro-inflammatory Th17 cells, whereas butyrate and propionate induce anti-inflammatory Treg cells by GPRs or inhibition of histone deacetylases [59, 60].

Gut Microbiota Changes the Serotonin

Serotonin (5-HT) is a neurotransmitter with diverse functions and more than 95% of 5-HT in the body could increase arterial contractility and smooth muscle growth, causing disease of hypertension. Increasing serotonin also regulates blood pressure through reduction of sodium excretion by the kidney and promoting cardiac hypertrophy [61–64]. Serotonin can activate the vagus and sympathetic nerve [65]. Vagus nerve can decrease blood pressure, but the activation of sympathetic nerve can cause high blood pressure. When the sympathetic nerve overactivated, serotonin will increase blood pressure.

Studies have found that intestinal microbiota can affect the synthesis, secretion, and function of serotonin. GF mice have reduced serotonin in serum, colon, and feces when compared to HM mice (GF mice colonized with human gut microbiota) [66, 67]. And studies with GF mice found that the decrease of colon 5-HT is due to the decrease expression of tryptophan hydroxylase 1 (TPH1) that are the rate-limiting enzymes for 5-HT biosynthesis [66]. Spore-forming bacteria (Sp) promote 5-HT biosynthesis from colonic ECs through elevation of particular metabolites such as deoxycholate, α -tocopherol, PABA, and tyramine [68]. Mandić et al. found that *Clostridium ramosum* could promote differentiation of intestinal stem progenitors toward the secretory 5-HT-producing lineage and stimulate 5-HT secretion from enterochromaffin

cells [67]. The gut microbiota and its metabolites such as SCFAs and BAs can induce ECs to secrete serotonin [66, 68]. SCFAs induce TPH1 expression to produce 5-HT in a model of human ECs [66]. But this requires a proper concentration of SCFAs, high concentration will have an inhibitory effect. There are research report *E. coli* K12 in the gut can produce serotonin [69].

Gut Microbiota Changes in High-Salt-Induced Hypertension

High-salt diet (HSD) is an important risk factor for hypertension. In humans and mice, high-salt intake leads changes in the gut microbiota. High-salt intake increased ratio of Firmicutes to Bacteroidete, enriched *Lachnospiraceae*, *Proteobacteria*, *Verrucomicrobia*, and *Prevotella spp.* [70–72] A high-salt diet can also significantly reduce the *Lactobacillus* in the intestine. *Lactobacillus* can metabolize tryptophan into indole and then inhibit the differentiation of T lymphocytes into Th17 cells, improving inflammation and lowering blood pressure. The decrease in *Lactobacillus* could lessen the production of indole and increase blood pressure [7, 73].

Under normal circumstances, the intestinal *Bacteroides fragilis* could inhibit the production of intestinal-derived corticosterone through its metabolite arachidonic acid (AA). However, HSD reduced the levels of *B. fragilis* and AA in the intestine, which increased intestinal-derived corticosterone production and raised corticosterone levels in serum and intestine, thereby promoting BP elevation [72]. Elevated corticosterone levels lead to salt-induced sympathetic excitation, changes in sodium handling, and vascular resistance [74, 75].

The Link Between Antihypertensive Drugs and Gut Microbiota

The Effects of Intestinal Bacteria on Antihypertensive Drugs

There are trillions of intestinal microbes in the intestine, which can have a huge effect on the metabolism of many xenobiotics mediated by gut microbial enzymes [76]. Studies have shown that the intestinal microbiota can exert various metabolic capabilities, and regulates the biotransformation of oral drugs in the gastrointestinal tract [77, 78]. These changes may have a greater impact on long-term oral medications. Antihypertensive drugs undergo biotransformation by intestinal flora, and their absorption in the intestinal tract may be changed, leading to changes in its pharmacological potency. Antihypertensive drugs can also induce different behaviors of the gut microbiota of rats and human (Table 2). Amlodipine is a representative calcium channel blocker and one of the most

frequently prescribed drugs for the treatment of hypertension. Yoo et al. combined amlodipine incubated with human and rat feces to investigate whether the drug was metabolized by intestinal microbial enzymes [79]. In the human and rat feces samples, the remaining amlodipine decreased gradually as the incubation time increased [79]. In this case, gut microbiota might play a role in the biotransformation of amlodipine and could eventually affect the pharmacokinetics of drugs. Another calcium channel blocker diltiazem has also proved to be primarily eliminated by the intestinal flora. Zimmermann et al. measured the ability of 76 diverse human gut bacteria to metabolize 271 oral drugs and found that many of these drugs are chemically modified by microbes, and diltiazem can be metabolized by *Bacteroides thetaiotaomicron* [12]. Even though the metabolism of antihypertensive drugs by gut microbial enzymes has been recognized to some extent, there is still limited information about the specific microbial groups that mediate each metabolic reaction.

However, regulating the intestinal flora may also increase the bioavailability of antihypertensive drugs. Zhang et al. [80] attempt to prove whether the intestinal flora is involved in the metabolism of nifedipine in rats, through the plateau hypoxia to modulate the bioavailability and therapeutic efficacy of nifedipine by altering the metabolic activity of the gut microbiota. The results showed that the metabolic rate of nifedipine in the plain group was twice that of the plateau group and demonstrates that plateau hypoxia could attenuate the metabolic activity of intestinal flora to enhance the bioavailability of nifedipine. Researches have shown that probiotic *Lactobacillus casei* can affect the intestinal metabolic extraction of nifedipine [83]. In that study, the maximum concentration of nifedipine in plasma after administration into the intestinal loop (0.8 mg/kg) was significantly higher in *L. casei*-treated rats (3.26 µg/mL) than in those untreated rats (2.33 µg/mL) by 40%. And combining amlodipine and ampicillin, the plasma concentration levels of amlodipine were noticeably elevated in the ampicillin-treated rats, indicating an increase in its bioavailability [79]. Therefore, the decrease in the formation rate of amlodipine metabolites in the fecal enzymes of antibiotic-treated rats indicates that the increased plasma amlodipine level in antibiotic-treated rats may be due to the reduction of amlodipine microbial transformation in the gastrointestinal tract.

The Effects of Antihypertensive Drugs on Intestinal Bacteria

Several studies have attempted to purposely manipulate gut microbiota in animal models in order to determine whether this can alter blood pressure regulation, and/or to determine whether gut microbiota levels may change in hypertensive models. For example, a recent study found that gavage captopril in SHR rats increased the abundance of *Coprococcus*

Table 2 Antihypertensive drugs induce different behaviors of the gut microbiota of rats and human and the influence of intestinal bacteria on the metabolism of antihypertensive drugs.

Reference	Research object	Antihypertensive drugs	Increased genus	Gut microbiota index	Intestinal pathophysiology	Sympathetic activity	Fecal incubation
Santisteban et al. [10••]	SHRs	Captopril	-	-	Villi length↑ Fibrotic area↓ Thickness of the muscularis layer↓ Goblet cell numbers↑	-	-
Zimmermann et al. [12]	Bacteroides thetaiotaomicron	Diltiazem	-	-	-	-	Diltiazem↓
Yang et al. [13]	SHRs	Captopril	<i>Allobaculum</i> <i>Mucispirillum</i> <i>Parabacteroides</i>	Chao richness↑ Observed OUT↑ Shannon diversity↑ Simpson diversity↑	Fibrotic area↓ Villi length↑ Goblet cell numbers↑ I-FABP↓	↓	-
Robles-Vera et al. [14]	SHRs	Losartan	<i>Verrucomicrobiaceae</i> <i>Pedobacter</i> <i>Akkermansia</i>	Firmicutes/Bacteroidetes ratio↓ The percentage of anaerobic bacteria↑	Intestinal integrity↑ (occluding; ZO-1; MUC-2; MUC-3)	↓	-
	SHRs	Hydralazine	-	Firmicutes/Bacteroidetes ratio↑	Intestinal integrity↓	↑	-
Yang et al. [34••]	SHRs	Minocycline	<i>Akkermansia</i> <i>Bacteroides</i> <i>Enterorhabdus</i> <i>Marvinbryantia</i>	Shannon diversity↓ Fecal biomass DNA/feces↓ Chao richness↑ Pielou evenness↑ Shannon diversity↑	Villi length↑ Fibrotic area↓ Thickness of the muscularis layer↓ Goblet cell numbers↑	-	-
Yoo et al. [79]	Human	Amlodipine	-	-	-	-	Amlodipine↓
Zhang et al. [80]	Wistar rats	Nifedipine	-	-	-	-	Nifedipine↓
Li et al. [81••]	Pregnant SHRs	Captopril	<i>Coproccoccus</i> <i>Oscillospira</i> <i>Roseburia</i> <i>Dehalobacterium</i>	Shannon diversity↑ Firmicutes/Bacteroidetes ratio↓	-	-	-
	SHR male offspring	Captopril	<i>Allobaculum</i> <i>Anaerostipes</i> <i>Coproccoccus</i> <i>Oscillospira</i> <i>Roseburia</i> <i>Dehalobacterium</i> <i>Lactobacillus</i>	-	Intestinal integrity↑ (tight junction protein 1; occluding; claudin 4)	↓	-
Wu et al. [82••]	SHRs	Candesartan	-	Firmicutes/Bacteroidetes ratio↓	Intestinal integrity↑ (cingulin; occluding; tight junction protein 1)	-	-

SHRs spontaneously hypertensive rats

thought to be butyrate-producers, and also lowered blood pressure [81••]. The specific microbial populations and their corresponding metabolites, such as SCFAs, have direct and/or indirect effects on blood pressure. Studies have shown that antihypertensive drugs may exert antihypertensive effects by changing intestinal homeostasis. The impairment of lactic acid-producing *Lactobacillus* is associated with pathological progression of hypertension, but candesartan treatment leads to the remarkable preservation of *Lactobacillus* in SHR rats while lowering blood pressure [82••]. It is possible that candesartan may decrease hypertension by preserving the gut abundance of *Lactobacillus*, which warrants further clarification in future studies. And losartan treatment tended to restore changes in *Verrucomicrobiaceae*, *Pedobacter*, and *Akkermansia* and significantly restored changes in *Lactobacillaceae* and *Lactobacillus* [14]. Furthermore, minocycline, a broad-spectrum anti-inflammatory antibiotic, has been shown to lower blood pressure in Ang-II-infused rats [84]. Interestingly, oral administration of minocycline did not result in a further reduction of bacterial load but increased *Bacteroidetes* in the gut. So, whether antihypertensive drugs worked by regulating a specific intestinal flora. These results could not be directly extrapolated to other antihypertensive drugs but suggest that antihypertensive drugs may act by regulating the intestinal flora. If the gut microbiota is indeed involved in drug responses in hypertension, pinpointing the specific strains involved is essential for understanding the underlying mechanisms, and to develop novel therapeutic targets.

The Effects of Antihypertensive Drugs on Intestinal Bacteria Metabolites

Nifedipine

Nifedipine, a dihydropyridin calcium channel, is mostly utilized for the clinical treatment of precordial angina, hypertension, and other vascular diseases. Researches have shown that nifedipine may exert antihypertensive effects by affecting the metabolites of intestinal microbes.

Flavonoids are a diverse group of bioactive polyphenolic compounds widely distributed in many dietary plant materials and are ingested in considerable amounts with food. Flavonoids have significant antioxidant activity and can lower blood pressure through increasing nitric oxide (NO) bioavailability, reducing endothelial cell oxidative stress, or modulating vascular channel activity, and are mainly metabolized by *Clostridium orbiscindens* in the intestine [85, 86]. A study found that after taking nifedipine in high-salt-induced hypertensive rats, the level of 3-(3-hydroxyphenyl) propionate (3-HPP) in the intestine is significantly increased [87]. 3-HPP is a representative product of intestinal bacteria metabolizing flavonoids such as quercetin and catechin. It has anti-

inflammatory, antioxidative stress, and calcium ion antagonism effects, and can significantly reduce blood pressure in SHR rats [88]. Whether 3-HPP is related to the curative effect of nifedipine requires further research.

Nifedipine can significantly reduce the intestinal deoxycorticosterone level of hypertensive rats induced by high salt [87]. In the previous study, it was reported that increased production of corticosterone and decreased plasma cortisol level play a pathogenetic role in the blood pressure increase [89, 90]. Studies have found that *Bacteroides fragilis* in the intestinal flora can decrease the level of corticosterone produced by the intestinal epithelium through its metabolite arachidonic acid, which plays an important role in the pathogenesis of high-salt hypertension [72]. It shows that the intestinal flora can play a hypotensive effect by regulating steroid hormones. However, the studies have not shown that nifedipine increases the number of *Bacteroides fragilis*, the mechanism by which nifedipine increases the production of arachidonic acid to reduce the level of corticosterone to exert its antihypertensive effect is unknown.

BAs are derived from cholesterol oxidized by enzymes in the liver and it can also be metabolized by the intestinal flora, which can increase the diversity of BAs and the hydrophobicity of the BA pool to promote the fecal excretion of BAs. It can not only promote the digestion and absorption of dietary fat but also act as a hormone to activate different receptors, including farnesoid X receptor (FXR), G protein-coupled receptor (TGR5), pregnane X receptor (PXR), and vitamin D receptor. Studies have shown that the intestinal flora plays an important role in the metabolism of bile acids that they can convert primary bile acids produced in the liver into secondary bile acids, such as *Clostridium* (XIVa and XI clusters) and *Eubacterium* belonging to Firmicutes [91]. Studies have found that compared with normal intestinal flora rats, the levels of BAs in various tissues of GF rats are significantly increased, and rats treated with antibiotics also show a decrease in BAs metabolism [92]. Therefore, the intestinal flora may regulate the activity of receptors such as PXR by regulating the metabolism of BAs. With the deepening of research, it was discovered that PXR is involved in the transcription and activation of cytochrome P450 (CYP) 3A4 enzyme [93]. Nifedipine is a substrate of CYP3A4 enzyme, whether the intestinal flora can change the activity of PXR receptors by affecting the metabolism of bile acids, and further cause changes in the metabolism of nifedipine by the CYP3A4 enzyme, and thus affect the efficacy, remains to be further studied.

Candesartan

Candesartan is an angiotensin II type 1 receptor blockers (ARBs), first-line antihypertensive drugs extensively used for the treatment of hypertension. A recent study showed that

SHRs were found a significantly increased fecal amount of acetic acid, propionic acid, and butyric acid after 14 weeks of candesartan treatment [82••]. There is evidence that the gut microbiota exerts important influences on the regulation of blood pressure by signaling through metabolic byproducts such as SCFAs, which enter the bloodstream via colonic absorption [44]. In general, it appears that increased SCFAs are associated with lower blood pressure. However, although the blood pressure is tightly controlled after 6-week treatment of candesartan, but no significant increase in the fecal amount of acetic acid was observed [82••]. Therefore, these results can only suggest that prolonged treatment of candesartan is beneficial for the microbial production of SCFAs, providing additional understanding of the antihypertensive and intestinal protective effects of candesartan. The mechanisms underlying the beneficial effects of candesartan on the microbial production of SCFAs need further explanation.

Effects of Antihypertensive Drugs on Intestinal Pathophysiology

In recent years, studies have found that there is a symbiotic relationship between the intestine and its flora, and the hypotensive effect of hypotensive drugs may be related to the improvement of intestinal pathophysiology. This intestinal pathology may in turn further lead to host-intestinal flora symbiosis imbalance and cause a variety of diseases, such as obesity, nervous system disorders, chronic kidney disease, inflammatory bowel disease (IBD), and cardiovascular disease (CVD) [94, 95]. Mohan K. Raizada and colleagues found increased permeability and stiffness in the small intestine and proximal colon, decreased levels of tight junction proteins, increased gut fibrosis, thickening of the gut muscularis layer, decreased villi length, and goblet cell loss in SHRs and in rats with Ang-II-induced hypertension [10••]. After the treatment of captopril, the gut permeability was reduced, and fibrosis levels and thickness of the muscularis layer were completely restored [10••]. At the same time, mean arterial pressure also dropped significantly [10••]. Another study showed that decreased blood pressure, altered gut microbiota, improved gut pathology, and permeability were maintained even after the withdrawal of this ACEi [13]. Losartan changes in microbiota induced by it were independent of its blood pressure reducing effects and seemed to be related to the improvement of gut integrity [14]. SHR treated with losartan showed increase colonic integrity and a proportion of strict anaerobic bacteria similar to Wistar-Kyoto (WKY) rats, whereas hydralazine was unable to improve both gut integrity and the proportion of anaerobic bacteria. Furthermore, they found SHRs have reduced mRNA levels of barrier-forming junction proteins (Ocln and ZO-1) and downregulated of mucin (MUC)-2 transcripts and increased intestinal permeability. Interestingly, losartan can restore occludin and ZO-1 mRNA

levels in the colon and reduced gut permeability [14]. Then, changes induced by losartan in gut microbiota contributed, at least in part, to protecting the vasculature and reducing blood pressure. Another angiotensin receptor antagonist, candesartan, can reduce the area and damage of SHRs colon and ileum fibrosis, and maintain the integrity of the intestine [82••].

The Effect of Antihypertensive Drugs on Intestinal Inflammation

The intestine is the largest immune organ with a complex mucosal immune system located at its inner surface and exposed to the lumen [53]. Nearly half of the immune cells are attached to the intestine, such as macrophages and dendritic cells, and produce 80% of the body's antibodies [96]. The gut microbiota may have a critical role not only in determining local immune outcomes but also in maintaining systemic physiology. Therefore, the changes in gut microbiota may lead to abnormal central immunity. Studies have shown that the increase in inflammation of the intestinal epithelium of SHRs is related to the increase in blood pressure [10••]. Hong-Bao Li et al. after giving captopril to pregnant female SHRs and their offspring, the intestinal bacteria of the offspring receiving and not receiving captopril can be significantly improved [81••]. When the offspring grow to 12 weeks of age, Cd3, Cd68, TNF, IL-1b, IL-6, TLR2 (toll-like receptor 2), TLR4 (toll-like receptor 4), and Rage (receptor for advanced glycation end products) of offspring were all lowered compared with SHRs [81••]. Furthermore, long-term treatment with losartan significantly decreased endotoxemia in SHR, and the increased mRNA levels of the colonic pro-inflammatory cytokines TNF- α , IL-6, IL-17, and IFN- γ in SHR were significantly reduced [14]. Losartan also can increase the Treg population in mesenteric lymph nodes (MLNs), without affecting the Th17 cell population [14].

The Effect of Antihypertensive Drugs on the Nervous System

The gut enteric nervous system is complex and capable of functioning independently of extrinsic inputs. Norepinephrine and sympathetic nerves can regulate the migration and accumulation of lymphocytes in the intestine [97]. The vagus nerve and sympathetic nerve are related to the intestinal barrier function. Therefore, the nervous system is very important in regulating intestinal immunity and intestinal epithelial barrier function [98, 99]. However, studies have shown that the increase of BP in the SHR has been closely associated with increased sympathetic activity and activation of microglia. These increases were significantly attenuated by continuous captopril treatment [10, 81]. Early studies have also shown that the antihypertensive effect of captopril is

maintained in SHR male offspring long after the withdrawal of captopril, and ameliorated the dysfunctional gut-brain axis could be one such mechanism [13]. Losartan can block sympathetic drive of SHRs, and this effect related to the changes in the intestinal flora induced by it [14]. Therefore, the gut microbiota and its products are related to the sympathetic nerve activation, and brain-gut communication exists [53].

Future Directions

In this review, we give an overview of the relationship between hypertension and intestinal flora and the interaction between the efficacy of antihypertensive drugs and intestinal flora. Data from numerous studies have shown that changes in intestinal flora are closely related to development and maintenance of hypertension. Generally, in hypertensive animals and patients, the composition and abundance of gut microbiota, metabolites of intestinal flora, and intestinal pathophysiology will change. Using antihypertensive drugs to treat hypertension is one of the most effective methods at present. Recently, studies have shown that the intestinal flora can affect the pharmacokinetics and metabolism of antihypertensive drugs in the rats, and intestinal microbiota also can be the target “organ” by antihypertensive drugs. The presence of intestinal microbes in the human body can accelerate the metabolism of antihypertensive drugs. Animal-level studies have found that antihypertensive drugs can change the composition of intestinal flora and restore intestinal microbial homeostasis, improve intestinal pathology, brain-gut axis, and reduce intestinal inflammation while reducing blood pressure. Some antihypertensive drugs can also affect the metabolites of intestinal flora, such as increase the level of SCFAs, BAs, and AA. These gut microbiota metabolites are related to the occurrence and development of hypertension.

However, whether the individual difference of antihypertensive drugs’ efficacy can partly explain by individual differences of intestinal flora remains to be further explored. The relative concentrations of individual bile acids and composition of intestinal flora of different mammals can vary significantly [100]. The existing researches of the relationship between antihypertensive drugs and gut microbiota are focused on animal experiments, there is still a lack of large-scale clinical trials, and the results of animal-level experimental can only serve as a reminder for the clinic. Therefore, it is necessary to be cautious when transferring from animal-level research results to humans. More importantly, human studies are needed to understand the mechanism of interaction between gut microbiota and antihypertensive drugs, and whether (or which) gut microbiota is causally linked to antihypertensive drugs metabolism in humans.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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