Postprint: Mechanistic Study of High-Salt-Induced Gut Microbiota Dysbiosis Regulating Salt-Sensitive Blood Pressure

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Abstract

Excessive salt intake is one of the major risk factors for hypertension and cardiovascular disease. Salt-sensitive blood pressure (SSBP) exists in the population, and its impact on blood pressure is greater in hypertensive patients than in normotensive individuals. In recent years, in-depth studies on the gut microbiota have revealed significant connections among gut microbiota, blood pressure, and salt intake, with gut microbiota playing a crucial role in the onset and progression of SSBP. In this review, we will explore the potential mechanisms by which a high-salt diet induces dysregulation of gut microbiota and its metabolites and immune cell involvement in SSBP, providing a novel perspective for the prevention and treatment of SSBP through modulating gut microbiota homeostasis and associated immune-inflammatory pathways.

Full Text

Mechanisms of High Salt-Induced Gut Microbiota Disturbances in Regulating Salt-Sensitive Blood Pressure

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Abstract

Excessive salt intake is one of the major risk factors for hypertension and cardiovascular disease. Salt-sensitive blood pressure (SSBP) exists in the population and has a greater impact on blood pressure in hypertensive patients than in normotensive patients. In recent years, in-depth research on the gut microbiota has demonstrated a significant relationship between gut microbiota, blood pressure, and salt intake, revealing that gut microbiota plays an important role in the occurrence and development of salt-sensitive blood pressure. In this review, we explore the possible mechanisms by which a high-salt diet leads to dysregulation of gut microbiota and its metabolites, as well as the involvement of immune cells in SSBP, providing new insights into the prevention and treatment of SSBP through modulation of gut microbiota homeostasis and associated immune-inflammatory pathways.

Keywords: high salt; gut microbiota; hypertension; salt sensitivity; mechanism

Introduction

Hypertension is one of the major risk factors for cardiovascular events and represents an increasingly heavy medical burden. Recent survey data[1] show that the prevalence of hypertension in China is generally increasing, and its incidence is closely related to dietary habits and lifestyle. High salt intake is one of the major external risk factors for hypertension and cardiovascular disease[2]. A meta-analysis[3] demonstrated that salt restriction can lower blood pressure and reduce the annual incidence of new coronary heart disease and stroke cases in the United States by 20%. However, a major problem with excessive salt intake is the existence of salt-sensitive blood pressure (SSBP) in a large number of normotensive and hypertensive subjects. SSBP is an independent risk factor for cardiovascular disease mortality. Over the past decades, numerous studies have investigated the pathogenesis of SSBP, including the renin-angiotensin-aldosterone system, sympathetic nervous system, insulin resistance, endothelin, nitric oxide, reactive oxygen species, and dopamine, yet much remains unknown. In recent years, substantial research has established a potential link between gut microbiota and blood pressure, with dietary salt intake being one of the triggering factors. Mell et al.[4] first demonstrated in Dahl salt-sensitive and salt-resistant rats that dietary salt could regulate blood pressure through gut microbiota. Several recent studies[5-7] have confirmed that gut microbiota and immune cells can sense Na+, leading to inflammation and hypertension. Given the clear connection between sodium, gut microbiota, and hypertension, understanding the effects of sodium on gut microbiota and blood pressure is imperative.

Salt intake can alter the composition and function of gut microbiota. Mell et al.[4] confirmed that high salt regulates blood pressure in a gut microbiota-dependent manner. High-salt diet reduces the abundance of *Lactobacillus* species, leading to decreased levels of indole-3-lactic acid (ILA), which normally inhibits TH17 cell activation, thereby causing TH17 cell activation and elevated blood pressure. When mice return to a normal diet, *Lactobacillus* levels normalize and blood pressure decreases. Administration of *Lactobacillus murinus* to salt-sensitive rats fed a high-salt diet significantly reduces their blood pressure (BP) and inhibits TH17 cell activation[8]. These findings suggest the existence of a salt-*Lactobacillus*-SSBP regulatory mechanism. *Lactobacillus* has anti-inflammatory effects, inhibits pathogen growth and Th17 cell activation, and modulates gut microbial structure and composition, conferring benefits to the host. In addition to *Lactobacillus*, *Clostridium* species have also been shown to be greatly affected by high salt. Bier et al.[9] demonstrated in salt-sensitive rats that Christensenellaceae, Eubacteriaceae, and Anaerofustis (all subgroups of *Clostridium*) were positively correlated with BP under high-salt diet (HSD), while the genus *Anaerostipes* was negatively correlated with BP. Wang et al.[10] observed that during an 8-week high-salt diet, the Firmicutes/Bacteroidetes ratio, Lachnospiraceae, and Ruminococcus increased, exacerbating colitis in mice. When mice were fed a normal-salt diet, greater within-group differences in bacterial species were observed, indicating that high-salt diet is associated with lower microbial diversity and that bacterial species have different salt tolerance.

The sodium/hydrogen exchanger 3 (NHE3) is present in renal proximal tubules and the gastrointestinal tract, regulating sodium and water absorption[11]. The intestinal mucosa is the first and primary site of excess salt absorption. Sodium is highly absorbed in the colon via NHE3. Linz et al.[12] demonstrated that in spontaneously hypertensive rats, administration of NHE3 inhibitors increased fecal sodium and water content, reduced urinary sodium excretion, and lowered blood pressure. Two studies in NHE3 knockout mice[13,14] found altered gut microbiota composition and diversity (i.e., decreased Firmicutes/Bacteroidetes ratio) and reduced blood pressure. These results suggest that gut microbiota likely participates in systemic salt uptake and responds to salt-sensitive blood pressure.

High-salt diet promotes changes in the intestinal microecological environment, leading to gut microbiota dysbiosis. The resulting metabolites can trigger chain reactions, creating a vicious cycle that severely affects blood pressure. Gut microbiota metabolites include short-chain fatty acids (SCFAs), trimethylamine-N-oxide (TMAO), bile acids (BAs), hydrogen sulfide (H_2S), tryptophan (Trp), among others. The possible mechanisms by which these metabolites contribute to salt-sensitive blood pressure are described below.

2.1 Short-Chain Fatty Acids (SCFAs) Pathway

Under high-salt conditions, concentrations of SCFAs (such as acetate, propionate, and butyrate) change. Animal model studies[15,16] have shown that SCFAs can lower blood pressure. For instance, in spontaneously hypertensive rats (SHR) and deoxycorticosterone acetate (DOCA)-salt rats, high-fiber diet and acetate and propionate supplementation significantly reduced blood pressure levels. Chen et al.[17] found that salt reduction increased circulating SCFAs in humans, which influenced the gut microbiota. Increased SCFA levels, in turn, lowered blood pressure and improved arterial compliance. This may be because low-salt diet affects gut microbiota in hypertensive patients, as almost all circulating SCFAs originate from gut microbiota. Research has shown[18] that SCFAs bind to different G protein-coupled receptors (GPCRs), exerting varied effects on blood pressure regulation, primarily including G protein-coupled receptor 41 (GPR41), G protein-coupled receptor 43 (GPR43), G protein-coupled receptor 109A (GPR109A), and olfactory receptor 78 (Olfr78). Natarajan et al.[19] confirmed in animal experiments that GPR41 is mainly expressed in vascular endothelial cells, and binding with propionate causes vasodilation and lowers blood pressure. Another study[20] showed that GPR41 is also expressed in sympathetic ganglia in mice and humans, and SCFAs activate the sympathetic nervous system via the GPR41/G$\beta\gamma$/PLCβ/MAPK signaling pathway, promoting ERK1/2 phosphorylation to regulate blood pressure. Additionally, SCFAs activate the GPR43 receptor, which can repair intestinal epithelium[21] and reduce inflammatory immune responses[22], both of which have positive effects on blood pressure. Olfr78 is expressed in blood vessels and renal afferent arterioles (smooth muscle cells); SCFAs binding to Olfr78 promote renin secretion and increase blood pressure[15]. GPR109A is expressed in the rostral ventrolateral medulla, and activation by its ligand niacin in immune cells increases Ca^{2+} levels, which induces glutamate release and oxidative stress in central blood pressure regulatory nuclei, leading to elevated blood pressure[23].

2.2 Trimethylamine N-Oxide (TMAO) Pathway

Gut microbiota metabolizes foods rich in phosphatidylcholine, choline, and L-carnitine into trimethylamine (TMA), which enters the portal circulation and is oxidized by flavin monooxygenases (primarily the FMO3 isoform) in the liver to produce TMAO[24]. Previous studies in animals and humans[18] have elucidated the role of TMAO in promoting atherosclerosis, thrombosis, heart failure, insulin resistance, and kidney disease, all of which are predisposing factors for hypertension. In endothelial and smooth muscle cells, TMAO rapidly activates mitogen-activated protein kinase (MAPK) and nuclear factor kB (NF-kB) to promote expression of adhesion molecules such as intercellular adhesion molecule (ICAM) and E-selectin. Furthermore, TMAO can promote fibrosis in the heart and kidneys through the transforming growth factor β (TGFβ)-phosphorylation-SMAD3 signaling axis[25].

An animal study[26] demonstrated that compared with rats infused with angiotensin II (AngII) alone, rats infused with AngII + TMAO showed a prolonged hypertensive response. Liu et al.[27] confirmed that *Lactobacillus rhamnosus* GG strain mitigated the development of obstructive sleep apnea-induced hypertension under high-salt diet by regulating TMAO levels and CD4 T cell-induced type I inflammation. Recent human research[28] indicates that TMAO induces aortic stiffness and increases systolic blood pressure with aging. Jiang et al.[29] recently revealed that TMAO promotes AngII-induced vasoconstriction through the PERK/ROS/CaMKII/PLC$ $3 axis pathway.

2.3 Bile Acids (BAs) Pathway

Bile acids act as endocrine-like signaling molecules, participating in lipid metabolism, accelerating energy expenditure, delaying atherosclerosis, inhibiting inflammation, regulating microbiota homeostasis, and protecting the intestinal barrier[30]. Primary bile acids are converted to secondary bile acids by specific gut microbiota. Primary bile acids such as chenodeoxycholic acid (CDCA) and cholic acid (CA) are synthesized from cholesterol in the liver and conjugated with glycine (in humans) or taurine (in humans and mice). They are released into the intestine during feeding to promote absorption of fat-soluble vitamins, and more than 95% are reabsorbed at the terminal ileum. Unabsorbed bile acids are metabolized by gut microbiota in the colon to secondary bile acids such as deoxycholic acid (DCA) and lithocholic acid (LCA), which become signaling ligands for various receptors including Farnesoid X receptor (FXR), G protein-coupled bile acid receptor 1, and vitamin D receptor (VDR)[30]. Studies have shown that bile acids can influence gut microbiota structure, and conversely, gut microbiota affects bile acid metabolism, highlighting the interrelationship of the gut microbiota-BAs-host axis. Research indicates that bile acids can regulate lipid metabolism and exert antibacterial and anti-inflammatory effects through FXR[31], delaying the progression of atherosclerosis[32]. G protein-coupled bile acid receptor 1 (GPBAR1, also known as TGR5) is a bile acid ligand expressed in the gastrointestinal tract as well as in macrophages and T cells. GPBAR1 activation increases expression of cystathionine γ-lyase (CSE), an enzyme necessary for generating the vasodilator hydrogen sulfide[33]. In rats fed bile acids[34], significant changes in gut microbiota were observed, including increased Firmicutes and decreased Bacteroidetes, i.e., a dysregulated Firmicutes/Bacteroidetes ratio, mainly characterized by increased *Clostridium*, decreased *Bifidobacterium breve*, and decreased *Lactobacillus salivarius*. These findings have been replicated in rodents and humans with hypertension induced by high-salt diet. However, to date, no study has linked bile acids, dietary sodium, and gut microbiota. The potential mechanism by which dietary sodium affects bile acid metabolism may be through regulation of gut microbiota composition. As previously described, dietary sodium depletes *Lactobacillus* and *Clostridium*, both of which are components of secondary bile acid metabolism[35]. In summary, bile acids may mediate the effects of gut microbiota on blood pressure regulation, but the mechanisms remain to be elucidated.

2.4 Hydrogen Sulfide (H_2S) Pathway

Hydrogen sulfide is a key intracellular signaling molecule with widespread physiological activities. It is classified as endogenous or exogenous based on its source.

Endogenous H_2S is primarily synthesized from L-cysteine through the enzymatic activity of cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) in the cytoplasm and mitochondria, mainly produced by epithelial, vascular, and smooth muscle cells[36]. Studies[37] have shown that H_2S causes vasodilation and relaxes vascular smooth muscle by activating large-conductance calcium-dependent potassium channels (BKCa) in endothelium and calcium-activated channels in vascular smooth muscle, thereby lowering blood pressure. Chinese scholar Xu Mingxing et al.[38] demonstrated that H_2S can reduce levels of various inflammatory factors (primarily interleukin-6), dilate blood vessels, and lower blood pressure. In rodents and humans, the colonic microbiota is the largest source of H_2S. Shen et al.[39] found in germ-free mice that CSE activity and free hydrogen sulfide levels were significantly reduced in plasma, gastrointestinal tissues, and other tissues, further proving that hydrogen sulfide production is mediated by gut microbiota. Tomasova et al.[40] administered hydrogen sulfide donors intracolonically to rats, inducing peripheral vasodilation and lowering blood pressure. These findings demonstrate that gut-derived H_2S helps control blood pressure, indicating the existence of a gut microbiota-H_2S-blood pressure pathway. This hypothesis was confirmed in a recent study on Dahl salt-sensitive rats[41], which found that exogenous H_2S alleviated high-salt diet (HSD)-induced hypertension by attenuating the nuclear factor kB pathway and pro-inflammatory cytokine protein expression, improving oxidative stress, inflammation, and apoptosis in the hypothalamic paraventricular nucleus (PVN).

2.5 Tryptophan Metabolism Pathway

Tryptophan (Trp) and its metabolites have been shown to play key roles in cardiovascular disease (CVD)[42]. 5-hydroxytryptophan (5-HTP) is a tryptophan metabolite converted by tryptophan hydroxylase 1 (Tph1) into serotonin (5-hydroxytryptamine, 5-HT) in the intestine. Tph1 activity is largely regulated by gut microbiota, producing more than 90% of 5-HT in the body[43]. The cardiovascular responses produced by 5-HT are complex. Villalón et al.[44] showed that 5-HT causes bradycardia or tachycardia, hypotension or hypertension, and vasodilation or vasoconstriction through interactions with different receptors in the central nervous system (CNS), autonomic ganglia and postganglionic nerve endings, vascular smooth muscle, and endothelium. Indole is a tryptophan-derived metabolite produced by gut microbiota and is known to be an endogenous ligand of the aryl hydrocarbon receptor (AHR), a transcription factor whose endogenous signaling plays important roles in cardiac function, vascular development, and blood pressure regulation[45]. Huć et al.[46] demonstrated that indole and indoxyl sulfate (a hepatic metabolite of indole) caused hypertension when administered peripherally in rats, while indole produced hypotensive effects when administered intracerebroventricularly. Subsequent studies further proved that indole and indoxyl sulfate affect arterial blood pressure through peripheral and central mechanisms dependent on serotonin signaling.

Indolepropionic acid (IPA) also participates in blood pressure regulation in rodents, increasing myocardial contractility and vasoconstriction, leading to hypertension[47]. Using the Langendorff heart model in mice, dose-dependent myocardial contractility responses to IPA were demonstrated[48], along with reduced vasodilation associated with sodium nitroprusside[49] and acetylcholine pretreatment[47]. The vascular effects of IPA may be related to activation of the pregnane X receptor (PXR)[49]. Dou et al.[50] showed that indole-3-acetic acid (IAA) upregulates cyclooxygenase-2 (COX-2) through activation of the AhR/p38 MAPK/NF- B signaling pathway, and increases endothelial reactive oxygen species (ROS) and expression of inflammatory genes (IL-6, IL-8, ICAM-1), inducing endothelial inflammation and oxidative stress that contribute to hypertension.

3. Gut Microbiota Influences SSBP Through Inflammatory Immune Responses

Gut microbiota dysbiosis, characterized by reduced probiotic synthesis and increased harmful bacteria, produces various inflammatory factors that further damage the intestinal mucosal barrier, thereby affecting blood pressure changes. Wilck et al.[8] demonstrated in animal experiments that high-salt diet caused a significant reduction in intestinal *Lactobacillus* and increased $CD4^+$, IL-$17A^+$, TNF^+, and TH17 cells in the intestinal immune system, leading to salt-sensitive hypertension, with consistent results obtained in human trials. Supplementing high-salt diet mice with *Lactobacillus murinus* reduced TH17 cells and significantly lowered blood pressure. Recently, high sodium intake, particularly sodium ions, has been shown to activate TH17 cells[8,51], possibly due to reduced *Lactobacillus* leading to decreased ILA, which normally inhibits TH17 cell activation[8]. TH17 cells secrete pro-inflammatory IL-17, IL-6, IL-22, and TNF-α, serving as major regulators of immune responses that promote hypertension development.

In contrast to conventional mice, germ-free mice have greater numbers of anti-inflammatory T regulatory cells, which are negatively correlated with TH17 cells[53]. Furthermore, Ferguson et al.[5] found that high-salt diet caused severe intestinal and vascular inflammation in mice, significantly increasing the B7 ligand CD86 and inducing dendritic cells (DCs) to form isolevuglandin (IsoLG) adducts, which stimulated T cells to produce interferon-γ (IFN-γ) and interleukin-17A (IL-17A), causing gut microbiota dysbiosis and hypertension. Fecal transplantation from conventionally raised high-salt fed mice to germ-free mice readily increased inflammation and hypertension[5]. In summary, sodium-induced activation of TH17 cells and specific interleukins may be mediated by gut microbiota, and different microbial responses to salt may explain the variability in salt-sensitive blood pressure among populations.

4. Summary and Outlook

Although current animal models and clinical studies have shown that gut microbiota plays an important role in salt-induced inflammation and hypertension—

potentially through gut microbiota metabolic disorders, SCFAs, TMAO, BAs, H_2S, and inflammation—clinical research data remain limited and the interaction mechanisms are still controversial. Future in-depth studies are needed to clarify the exact mechanisms of the salt-gut microbiota-salt-sensitive hypertension interaction and to investigate individual differences in gut microbiota responses to salt.

In the future, modulating gut microbiota homeostasis and associated immune-inflammatory pathways may become a potential therapeutic approach for SSBP.

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Conflict of Interest: The authors declare no conflict of interest.

Literature Search Strategy: English keywords "salt; gut microbiota; hypertension; salt sensitivity" were used to search PubMed, Medline, Web of Science, and SCI-hub. Chinese keywords "盐、高血压、肠道菌群、盐敏感" were used to search CNKI, Wanfang Data Knowledge Service Platform, and Chinese Biomedical Literature Database. To prevent omissions, references from retrieved literature were also examined. The search period was from database inception to April 2022. Inclusion criteria: laboratory or clinical research articles containing subject terms related to salt, hypertension, gut microbiota, and salt sensitivity. Exclusion criteria: literature with insufficient data information, duplicate publications, unavailable full text, or poor literature quality.

References

[1] National Center for Cardiovascular Diseases. Report on Cardiovascular Health and Diseases in China 2020[J]. Journal of Cardiovascular and Pulmonary Diseases, 2021, (09): 885-889.

[2] Murray C J, Lopez A D. Measuring the global burden of disease[J]. N Engl J Med, 2013, 369(5): 448-457.

[3] He F J, Li J, Macgregor G A. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials[J]. Bmj, 2013, 346: f1325.

[4] Mell B, Jala V R, Mathew A V, et al. Evidence for a link between gut microbiota and hypertension in the Dahl rat[J]. Physiol Genomics, 2015, 47(6): 187-197.

[5] Ferguson J F, Aden L A, Barbaro N R, et al. High dietary salt-induced

dendritic cell activation underlies microbial dysbiosis-associated hypertension[J]. JCI Insight, 2019, 5(13).

[6] Van Beusecum J P, Barbaro N R, McDowell Z, et al. High Salt Activates CD11c(+) Antigen-Presenting Cells via SGK (Serum Glucocorticoid Kinase) 1 to Promote Renal Inflammation and Salt-Sensitive Hypertension[J]. Hypertension, 2019, 74(3).

[7] Elijovich F, Laffer C L, Sahinoz M, et al. The Gut Microbiome, Inflammation, and Salt-Sensitive Hypertension[J]. Curr Hypertens Rep, 2020, 22(10): 79.

[8] Wilck N, Matus M G, Kearney S M, et al. Salt-responsive gut commensal modulates T(H)17 axis and disease[J]. Nature, 2017, 551(7682): 585-589.

[9] Bier A, Braun T, Khasbab R, et al. A High Salt Diet Modulates the Gut Microbiota and Short Chain Fatty Acids Production in a Salt-Sensitive Hypertension Rat Model[J]. Nutrients, 2018, 10(9).

[10] Wang C, Huang Z, Yu K, et al. High-Salt Diet Has a Certain Impact on Protein Digestion and Gut Microbiota: A Sequencing and Proteome Combined Study[J]. Front Microbiol, 2017, 8: 1838.

[11] He P, Yun C C. Mechanisms of the regulation of the intestinal Na+/H+ exchanger NHE3[J]. J Biomed Biotechnol, 2010, 2010: 238080.

[12] Linz D, Wirth K, Linz W, et al. Antihypertensive and laxative effects by pharmacological inhibition of sodium-proton-exchanger subtype 3-mediated sodium absorption in the gut[J]. Hypertension, 2012, 60(6): 1560-1567.

[13] Engevik M A, Aihara E, Montrose M H, et al. Loss of NHE3 alters gut microbiota composition and influences Bacteroides thetaiotaomicron growth[J]. Am J Physiol Gastrointest Liver Physiol, 2013, 305(10): G697-711.

[14] Li X C, Soleimani M, Zhu D, et al. Proximal Tubule-Specific Deletion of the NHE3 (Na(+)/H(+) Exchanger 3) Promotes the Pressure-Natriuresis Response and Lowers Blood Pressure in Mice[J]. Hypertension, 2018, 72(6): 1328-1336.

[15] Pluznick J L, Protzko R J, Gevorgyan H, et al. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation[J]. Proc Natl Acad Sci U S A, 2013, 110(11): 4410-4415.

[16] Marques F Z, Nelson E, Chu P Y, et al. High-Fiber Diet and Acetate Supplementation Change the Gut Microbiota and Prevent the Development of Hypertension and Heart Failure in Hypertensive Mice[J]. Circulation, 2017, 135(10).

[17] Chen L, He F J, Dong Y, et al. Modest Sodium Reduction Increases Circulating Short-Chain Fatty Acids in Untreated Hypertensives: A Randomized, Double-Blind, Placebo-Controlled Trial[J]. Hypertension, 2020, 76(1): 73-79.

[18] Poll B G, Cheema M U, Pluznick J L. Gut Microbial Metabolites and Blood Pressure Regulation: Focus on SCFAs and TMAO[J]. Physiology (Bethesda),

2020, 35(4): 275-284.

[19] Natarajan N, Hori D, Flavahan S, et al. Microbial short chain fatty acid metabolites lower blood pressure via endothelial G protein-coupled receptor 41[J]. Physiol Genomics, 2016, 48(11): 826-834.

[20] Kimura I, Inoue D, Maeda T, et al. Short-chain fatty acids and ketones directly regulate sympathetic nervous system via G protein-coupled receptor 41 (GPR41)[J]. Proc Natl Acad Sci U S A, 2011, 108(19): 8030-8035.

[21] D' Souza W N, Douangpanya J, Mu S, et al. Differing roles for short chain fatty acids and GPR43 agonism in the regulation of intestinal barrier function and immune responses[J]. PLoS One, 2017, 12(7): e0180190.

[22] Lanis J M, Alexeev E E, Curtis V F, et al. Tryptophan metabolite activation of the aryl hydrocarbon receptor regulates IL-10 receptor expression on intestinal epithelia[J]. Mucosal Immunol, 2017, 10(5): 1133-1144.

[23] Rezq S, Abdel-Rahman A A. Central GPR109A Activation Mediates Glutamate-Dependent Pressor Response in Conscious Rats[J]. J Pharmacol Exp Ther, 2016, 356(2): 456-465.

[24] Li Yipeng. Research progress of trimethylamine oxide in common cardiovascular diseases in the elderly[J]. Practical Geriatrics, 2022, (01): 11-13.

[25] Xiao H H, Lu L, Poon C C, et al. The lignan-rich fraction from Sambucus Williamsii Hance ameliorates dyslipidemia and insulin resistance and modulates gut microbiota composition in ovariectomized rats[J]. Biomed Pharmacother, 2021, 137: 111372.

[26] Ufnal M, Jazwiec R, Dadlez M, et al. Trimethylamine-N-oxide: a carnitine-derived metabolite that prolongs the hypertensive effect of angiotensin II in rats[J]. Can J Cardiol, 2014, 30(12): 1700-1705.

[27] Liu J, Li T, Wu H, et al. Lactobacillus rhamnosus GG strain mitigated the development of obstructive sleep apnea-induced hypertension in a high salt diet via regulating TMAO level and CD4(+) T cell induced-type I inflammation[J]. Biomed Pharmacother, 2019, 112: 108580.

[28] Brunt V E, Casso A G, Gioscia-Ryan R A, et al. Gut Microbiome-Derived Metabolite Trimethylamine N-Oxide Induces Aortic Stiffening and Increases Systolic Blood Pressure With Aging in Mice and Humans[J]. Hypertension, 2021, 78(2).

[29] Jiang S, Shui Y, Cui Y, et al. Gut microbiota dependent trimethylamine N-oxide aggravates angiotensin II-induced hypertension[J]. Redox Biol, 2021, 46: 102115.

[30] Brown J M, Hazen S L. Microbial modulation of cardiovascular disease[J]. Nat Rev Microbiol, 2018, 16(3): 171-181.

[31] Tian M, Yan J, Li X. Role of bile acid receptors in non-alcoholic fatty liver disease[J]. Chinese Journal of Biochemistry and Molecular Biology: 1-12.

[32] Zhang Y, Wang X, Vales C, et al. FXR deficiency causes reduced atherosclerosis in Ldlr-/- mice[J]. Arterioscler Thromb Vasc Biol, 2006, 26(10): 2316-2321.

[33] Fiorucci S, Zampella A, Cirino G, et al. Decoding the vasoregulatory activities of bile acid-activated receptors in systemic and portal circulation: role of gaseous mediators[J]. Am J Physiol Heart Circ Physiol, 2017, 312(1): H21-h32.

[34] Islam K B, Fukiya S, Hagio M, et al. Bile acid is a host factor that regulates the composition of the cecal microbiota in rats[J]. Gastroenterology, 2011, 141(5): 1773-1781.

[35] Fiorucci S, Distrutti E. Bile Acid-Activated Receptors, Intestinal Microbiota, and the Treatment of Metabolic Disorders[J]. Trends Mol Med, 2015, 21(11): 702-714.

[36] Wallace J L, Wang R. Hydrogen sulfide-based therapeutics: exploiting a unique but ubiquitous gasotransmitter[J]. Nat Rev Drug Discov, 2015, 14(5): 329-345.

[37] Jackson-Weaver O, Osmond J M, Riddle M A, et al. Hydrogen sulfide dilates rat mesenteric arteries by activating endothelial large-conductance Ca^{2+}-activated K^+ channels and smooth muscle Ca^{2+} sparks[J]. Am J Physiol Heart Circ Physiol, 2013, 304(11): H1446-1454.

[38] Xu Mingxing, Liu Wenxiu, Liang Yuting, et al. Research progress of hydrogen sulfide in cardiovascular diseases[J]. China Journal of Modern Medicine, 2020, (21): 34-38.

[39] Shen X, Carlström M, Borniquel S, et al. Microbial regulation of host hydrogen sulfide bioavailability and metabolism[J]. Free Radic Biol Med, 2013, 60: 195-200.

[40] Tomasova L, Dobrowolski L, Jurkowska H, et al. Intracolonic hydrogen sulfide lowers blood pressure in rats[J]. Nitric Oxide, 2016, 60: 50-58.

[41] Liao Y, Fan Y, He Q, et al. Exogenous H(2)S Ameliorates High Salt-Induced Hypertension by Alleviating Oxidative Stress and Inflammation in the Paraventricular Nucleus in Dahl S Rats[J]. Cardiovasc Toxicol, 2022, 22(5): 477-491.

[42] Nitz K, Lacy M, Atzler D. Amino Acids and Their Metabolism in Atherosclerosis[J]. Arterioscler Thromb Vasc Biol, 2019, 39(3): 319-330.

[43] Yano J M, Yu K, Donaldson G P, et al. Indigenous bacteria from the gut microbiota regulate host serotonin biosynthesis[J]. Cell, 2015, 161(2): 264-276.

[44] Villalón C M, Centurión D. Cardiovascular responses produced by 5-hydroxytriptamine: a pharmacological update on the receptors/mechanisms involved and therapeutic implications[J]. Naunyn Schmiedebergs Arch Pharmacol, 2007, 376(1-2): 45-63.

[45] Zhang N. The role of endogenous aryl hydrocarbon receptor signaling in cardiovascular physiology[J]. J Cardiovasc Dis Res, 2011, 2(2): 91-95.

[46] Huć T, Nowinski A, Drapala A, et al. Indole and indoxyl sulfate, gut bacteria metabolites of tryptophan, change arterial blood pressure via peripheral and central mechanisms in rats[J]. Pharmacol Res, 2018, 130: 172-179.

[47] Konopelski P, Chabowski D, Aleksandrowicz M, et al. Indole-3-propionic acid, a tryptophan-derived bacterial metabolite, increases blood pressure via cardiac and vascular mechanisms in rats[J]. Am J Physiol Regul Integr Comp Physiol, 2021, 321(6): R969-r981.

[48] Gesper M, Nonnast A B H, Kumowski N, et al. Gut-Derived Metabolite Indole-3-Propionic Acid Modulates Mitochondrial Function in Cardiomyocytes and Alters Cardiac Function[J]. Front Med (Lausanne), 2021, 8: 648259.

[49] Pulakazhi Venu V K, Saifeddine M, Mihara K, et al. The pregnane X receptor and its microbiota-derived ligand indole 3-propionic acid regulate endothelium-dependent vasodilation[J]. Am J Physiol Endocrinol Metab, 2019, 317(2): E350-e361.

[50] Dou L, Sallée M, Cerini C, et al. The cardiovascular effect of the uremic solute indole-3 acetic acid[J]. J Am Soc Nephrol, 2015, 26(4): 876-887.

[51] Kleinewietfeld M, Manzel A, Titze J, et al. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells[J]. Nature, 2013, 496(7446): 518-522.

[52] Shaw M H, Kamada N, Kim Y G, et al. Microbiota-induced IL-1β, but not IL-6, is critical for the development of steady-state TH17 cells in the intestine[J]. J Exp Med, 2012, 209(2): 251-258.

[53] Ivanov, II, Frutos Rde L, Manel N, et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine[J]. Cell Host Microbe, 2008, 4(4): 337-349.

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