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Review Article

Unraveling the Gut-Heart Axis: Microbial Composition Impacting Hypertension

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ABSTRACT

Hypertension, a major global health concern, has recently been linked to the gut microbiota, a complex community of microorganisms that inhabit the gastrointestinal tract. Emerging research suggests that the gut microbiota plays a crucial role in blood pressure regulation through various mechanisms, including modulation of metabolic pathways, immune responses, and neurohumoral regulation. Dysbiosis, an imbalance in gut microbial composition, has been implicated in the onset and progression of hypertension, where alterations in the production of short-chain fatty acids, inflammatory mediators, and metabolites like trimethylamine-N-oxide (TMAO) and lipopolysaccharides (LPS) contribute to vascular dysfunction and elevated blood pressure. In addition to microbial imbalances, lifestyle factors such as diet, exercise, and natural medicines have shown therapeutic promise by positively influencing gut microbiota composition, thus aiding in hypertension management. In contrast, the indiscriminate use of antibiotics has been found to exacerbate hypertension by disrupting microbial diversity and triggering systemic inflammation. This review delves into the complex relationship between the gut microbiota and hypertension, emphasizing the role of microbiota-derived metabolites, immune modulation, and microbial interactions in regulating blood pressure. It highlights promising therapeutic approaches targeting gut health, including dietary modifications, probiotics, and fecal microbiota transplantation, while stressing the importance of further research to optimize microbiome-based interventions for hypertension management.

Keywords: Gut microbiota, Hypertension, Microbiota-derived metabolites

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INTRODUCTION

The gut microbiota, a complex ecosystem of microorganisms residing in the gastrointestinal tract, plays a pivotal role in regulating various physiological processes, including blood pressure. Emerging evidence suggests that the gut microbiota influences hypertension through multiple mechanisms, including modulation of metabolic pathways, immune responses, and neurohumoral regulation.[1,2] Disruption of gut microbial composition, termed dysbiosis, has been implicated in the development and progression of hypertension, with alterations in the production of short-chain fatty acids (SCFAs), inflammatory mediators, and metabolites such as trimethylamine-N-oxide (TMAO) and lipopolysaccharides (LPS) contributing to vascular dysfunction and elevated blood pressure.[3,4] Dietary factors, exercise, and natural medicines, including plant-derived compounds, have been shown to modulate gut microbiota composition and offer therapeutic potential in hypertension management.[5,6] In contrast, antibiotics, commonly used for bacterial infections, can induce dysbiosis and exacerbate hypertension by disrupting microbial diversity and increasing systemic inflammation.[7,8] This review article explores the intricate relationship between gut microbiota and hypertension, highlighting the role of microbiota-derived metabolites, immune responses, and microbial interactions in blood pressure regulation. Additionally, it discusses current and potential therapeutic strategies targeting gut microbiota to manage hypertension, emphasizing the need for further research to optimize micro-biome-based interventions.[9]

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Historical Perspectives on Gut Microbiota and Hypertension

Initial research focused on the role of gut microbiota in metabolic disorders such as obesity and diabetes, which is closely associated with hypertension.[10] Advances in sequencing technologies, enabled detailed profiling of gut microbiota, revealing differences in microbial diversity between hypertensive and normotensive individuals.[11]

Animal studies provided key insights, demonstrating that germ-free mice exhibit altered blood pressure regulation, which could be normalized by fecalmicrobiota transplantation (FMT) from healthy donors.[12] Human studies further confirmed, that hypertensive patients have reduced microbial diversity and an imbalance in beneficial and pathogenic bacteria, with an increase in pro-inflammatory taxa such as *Firmicutes* and *Proteobacteria*.[13,14] Additionally, metabolites like short-chain fatty acids (SCFAs) and trimethylamine-N-oxide (TMAO) were identified as mediators of gut microbiota-induced blood pressure regulation, influencing vascular tone and inflammation.[15]These findings have led to emerging therapeutic approaches, highlighting the gut as a novel target for hypertension management. Ongoing research continues to explore microbiota-based therapies to optimize blood pressure control and reduce cardiovascular risk.

Microbial Shifts in the Gut of Hypertensive Individuals

Hypertensive patients exhibit a decline in beneficial bacteria such as Lactobacillus, Bifidobacterium, and Akkermansia, which are essential for regulating blood pressure through the production of short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate. These SCFAs promote vasodilation, reduce inflammation, and maintain gut barrier integrity, but a decrease in these beneficial microbes impairs SCFA production, contributing to vascular dysfunction and systemic inflammation.[10,14] In contrast, an overgrowth of pro-inflammatory bacteria such as Prevotella, Enterobacter, and Klebsiella is commonly observed in hypertensive patients. These bacteria produce endotoxins like lipopolysaccharides (LPS), which trigger systemic inflammation, endothelial dysfunction, and arterial stiffness.[13,11] Additionally, elevated levels of trimethylamine-N-oxide (TMAO), a microbial metabolite derived from dietary choline and carnitine, exacerbate oxidative stress and vascular inflammation.[15,12] Changes in the Firmicutes-to-Bacteroidetes (F/B) ratio and disruptions in key metabolic pathways, including SCFA synthesis and bile acid metabolism, further contribute to hypertension.[16,17] These findings highlight the potential of microbiota-targeted therapies for hypertension management.[18,19]

Alterations in Gut Microbiota in Hypertensive Animal Models

Animal models of hypertension, including spontaneously hypertensive rats (SHR), Dahl salt-sensitive rats, and angiotensin II-induced hypertensive mice, provide crucial insights into gut micro-biota alterations and their role in hypertension. In SHR, a reduction in beneficial bacteria like Lactobacillus and Bifido-bacterium, which produce short-chain fatty acids (SCFAs) such as butyrate and acetate, is observed. SCFAs are essential for maintaining gut integrity and regulating immune responses, and their decline contributes to inflammation and vascular dysfunction.[10,11] In contrast, opportunistic bacteria such as Prevotella, Desulfovibrio, and Klebsiella increase, producing endotoxins like lipopolysaccharides (LPS) that activate Toll-like receptor 4 (TLR4), leading to vascular inflammation and oxidative stress.[13,20] Dahl salt-sensitive rats, when fed a high-salt diet, show a similar imbalance, with reduced SCFA-producing bacteria and increased Enterobacteriaceae, promoting gut permeability and hypertension.[21,22] Probiotic supplementation with Lactobacillus murinus restores microbial balance and lowers blood pressure.[23] Angiotensin II-induced hypertensive mice also exhibit reduced microbial diversity and altered Firmicutes-to-Bacteroidetes ratios, with increased inflammatory cytokines, further highlighting themicrobiota-hypertension link.[24] Additionally, fecalmicrobiota transplantation (FMT) from hypertensive to normotensive mice induces hypertension, showing a causal relationship.[25]

The Role of Gut Barrier Integrity in Hypertension Development

Clinical studies reveal elevated circulating LPS, lipopolysaccharide-binding protein (LBP), and zonulin in hypertensive patients, linking gut permeability with systemic inflammation.[26] Increased gut permeability induces endotoxemia, oxidative stress, and nitric oxide (NO) reduction, leading to endothelial dysfunction and hypertension.[27] Additionally, gut dysbiosis lowers short-chain fatty acids (SCFAs), crucial for gut barrier maintenance, worsening inflammation and hypertension.[13]

High-salt diets exacerbate gut barrier dysfunction by altering microbial composition, reducing SCFA-producing bacteria, and enriching pro-inflammatory microbes like *Enterococcus faecalis*.[28] Probiotics and prebiotics have shown promise in restoring gut integrity and reducing blood pressure.[21]

Gut Microbiota Dysbiosis as a Driver of Hypertension

A decline in SCFAs due to dysbiosis contributes to endothelial dysfunction and hypertension.[28] Dysbiosis also increases pro-inflammatory bacteria, which produce lipopolysaccharides (LPS), leading to gut barrier dysfunction and systemic inflammation via Toll-like receptor 4 (TLR4) signaling.[20, 29] Additionally, dysbiosis disrupts bile acid metabolism, altering farnesoid X receptor (FXR) and TGR5 signaling, which impacts vascular tone and cholesterol metabolism.[24] Elevated trimethylamine-N-oxide (TMAO) levels, due to microbial metabolism of choline and carnitine, further exacerbate hypertension by promoting oxidative stress and vascular inflammation.[15]

Animal studies confirm a causal role of dysbiosis in hypertension, as fecalmicrobiota transplantation from hypertensive to normotensive animals induces hypertension.[30] Increased Firmicutes-to-Bacteroidetes (F/B) ratios and RAAS activation further contribute to hypertension.[10] High-salt diets aggravate dysbiosis, reducing *Lactobacillus* species, while probiotic supplementation restores microbial balance and lowers blood pressure.[23]

The Role of Gut Microbiota in Blood Pressure Homeostasis

Gut microbiota contributes to the onset and progression of hypertension through multiple mechanisms outlined below:

Integrity of Gut Barrier and its Influence on Blood Pressure Control

The intestinal barrier, maintained by tight junction proteins (occludin, claudins, ZO-1), restricts harmful molecules from entering circulation. Dysbiosis, marked by reduced *Lactobacillus* and *Bifidobacterium*, increases gut permeability, allowing LPS to enter the bloodstream and activate TLR4, leading to systemic inflammation, oxidative stress, and endothelial dysfunction, all of which contribute to hypertension.[29,20]

Additionally, gut dysbiosis reduces short-chain fatty acid (SCFA) production, impairing gut barrier integrity and vasodilation

through GPCRs.[28,10] Disruptions in gut-derived metabolites also influence the RAAS, further elevating blood pressure.[13]

Gut Microbiota Structure and the Regulation of BP

Gut microbiota composition significantly influences blood pressure regulation through metabolic, immune, and neurohumoral pathways. Beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium* produce short-chain fatty acidswhich activate G-protein-coupled receptors to promote vasodilation, reduce inflammation, and inhibit sympathetic overactivity.[28,13]

Dysbiosis (reduced microbial diversity and increased pathogenic bacteria)elevates levels of pro-inflammatory metabolites, including lipopolysaccharides (LPS), trimethylamine-N-oxide (TMAO), and secondary bile acids, leading to endothelial dysfunction, oxidative stress, and arterial stiffness.[29,15] Fecalmicrobiota transplantation (FMT) from normotensive donors has been shown to lower blood pressure in hypertensive models, demonstrating gut microbiota'scausal role in hypertension.[30] Probiotics, prebiotics, and dietary fiber can help restore microbial balance, making gut microbiota modulation a promisingstrategy for blood pressure control.[23]

Regulation of Blood Pressure through Gut-derived Microbial Metabolites

The gut microbiota generates many metabolites, such as SCFAs, hydrogen sulfide (H2S), trimethylamine-N-oxide (TMAO), corticosterone, choline, bile acids (BAs), indolesulfate, LPS, etc. Among these, SCFAs, TMAO, BAs, H_2S, and LPS are significantly associated with the progression of hypertension.

SCFAs and Their Role in Modulating Blood Pressure

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, regulate blood pressure through vascular, immune, and neurohumoral mechanisms. Produced by gut microbiota (*Lactobacillus*, *Bifidobacterium*, *Faecalibacterium*) via fiber fermentation, SCFAs act on G-protein-coupled receptors (GPR41, GPR43) in vascular, renal, and immune tissues.[28,17]SCFAs promote vasodilation by activating endothelial nitric oxide synthase (eNOS) via GPR41, reducing vascular resistance and lowering blood pressure.[31] They also inhibit sympathetic nervous activity by modulating the gut-brain axis, reducing catecholamine release.[11] Additionally, SCFAs exhibit anti-inflammatory effects by inhibiting NF-êBsignalling and promoting regulatory T-cell differentiation, reducing endothelial dysfunction.[13]

SCFAs also suppress renin-angiotensin-aldosterone system (RAAS) activation, with butyrate down-regulating renal renin expression, preventing vasoconstriction and sodium retention.[10] By enhancing gut barrier integrity, SCFAs reduce endotoxemia, mitigating systemic inflammation linked to hypertension.[29] Targeting SCFA production via fibre intake, probiotics, and supplementation offers potential therapeutic strategies.

Impact of TMAO on Vascular Function and Hypertension

Trimethylamine-N-oxide (TMAO), a metabolite derived from dietary choline, phosphatidylcholine, and L-carnitine, is linked to hypertension via inflammatory, oxidative stress, and vascular dysfunction pathways. Gut bacteria metabolize these compounds into trimethylamine, that gets converted to TMAO by hepatic enzymes.[15,32] Elevated TMAO levels promote inflammation by activating NF-κB, increasing cytokines like IL-6 and TNF-α, leading to endothelial dysfunction and arterial stiffness.[33] TMAO also induces oxidative stress, impairing nitric oxide signalling and reducing vasodilation,[34,35] while modulating the RAAS to promote vasoconstriction and sodium retention.[36] Dietary modifications and probiotics may mitigate TMAO's hypertensive effects.

Mechanism of Bile acids (BAs) to regulate blood pressure

Bile acids (BAs), synthesized from cholesterol in the liver and modified by gut microbiota, regulate blood pressure through their effects on metabolism, inflammation, and vascular function. Primary BAs activate nuclear receptors like FXR and TGR5, which modulate the renin-angiotensin-aldosterone system and improve endothelial function, thereby reducing blood pressure.[37,38] FXR activation suppresses renin expression, while TGR5 promotes vasodilation through nitric oxide production.[39-41] Additionally, BAs influence gut microbiota, affecting blood pressure via metabolites like SCFAs and TMAO.BAs modulate microbial metabolism, promoting the production of short-chain fatty acids (SCFAs) that enhance vasodilation and reduce inflammation.[42]

Vascular Effects of H_2S in Blood Pressure Control

Hydrogen sulfide (H_2S), produced from L-cysteine plays a key role in blood pressure regulation through vasodilation, anti-inflammatory, and antioxidant effects.[43,44] H_2S activates K-ATP channels in vascular smooth muscle, promoting vasodilation and reducing blood pressure.[45] It also enhances NO bioavailabilityand reduces oxidative stress.[46] H_2S suppresses inflammation by inhibiting NF-κB and cytokine production, while also inhibiting the RAAS. Increasing H_2S through dietary sulfur-containing amino acids and probiotics could offer therapeutic benefits for hypertension.[47,48]

LPS and Its Effect on Hypertension Regulation

Dysbiosis increases gut permeability, allowing LPS (a component of Gram-negative bacteria)to enter the bloodstream and activate toll-like receptor 4 (TLR4) on immune and endothelial cells, triggering the release of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, impairing NO availability and increasing vascular resistance.[49,17] LPS also activates the renin-angiotensin-aldosterone system and stimulates sympathetic nervous system over-activation, further elevating blood pressure.[11,50] Targeting gut integrity through probiotics and dietary changes may reduce LPS-induced hypertension.[16,51]

Gut Microbiota Modulation as a Strategy for Hypertension Control

Investigating gut microbiota-targeted interventions could offer novel approaches for managing hypertension. Currently, key strategies for modulating gut microbiota include fecalmicrobiota transplantation, probiotic supplementation, antibiotic usage, dietary and exercise modifications, antihypertensive medications, and natural therapeutic compounds.

Fecal Microbiota Transplantation (FMT)

FMT is an emerging therapeutic approach for managing hypertension by restoring gut microbial balance. FMT involves transferring gut

microbiota from a healthy donor to a hypertensive recipient, leading to improved gut barrier integrity, reduced systemic inflammation, and modulation of metabolites such as short-chain fatty acids (SCFAs) and trimethylamine-N-oxide (TMAO), which influence blood pressure regulation.[52,11] Animal studies have shown that FMT from normotensive donors lowers blood pressure in hypertensive models by modifying gut microbiota composition and reducing inflammation.[12] Further clinical trials are needed to establish FMT as a viable antihypertensive therapy.

Probiotics

Probiotics, live beneficial microorganisms, have shown promise in managing hypertension by restoring gut microbiota balance, enhancing short-chain fatty acid (SCFA) production, and reducing systemic inflammation. Certain probiotic strains, such as *Lactobacillus* and *Bifidobacterium*, improve endothelial function by increasing nitric oxide (NO) bioavailability and lowering oxidative stress.[53,28] Probiotics also modulate the RAAS mechanism, reducing vasoconstriction and sodium retention.[54] Clinical studies suggest that regular probiotic consumption can lead to modest reductions in blood pressure; particularly in hypertensive individuals.[55] Further research is needed to optimize probiotic formulations for effective blood pressure control.

Antibiotics

Antibiotic-induced dysbiosis impairs the production of SCFAs, vital for vascular health and blood pressure regulation. Additionally, antibiotics may increase the translocation of endotoxins like lipopolysaccharides, promoting systemic inflammation and endothelial dysfunction. While antibiotics negatively impact gut microbiota, targeted, microbiome-modulating antibiotics may offer potential for hypertension management by restoring gut health and improving blood pressure regulation.[56-64]

Diet and Exercise

A fiber-rich, polyphenol-enriched diet promotes beneficial bacteria and SCFAs, regulating blood pressure. In contrast, a high-fat, high-sugar diet causes dysbiosis and inflammation. Exercise enhances microbial diversity, SCFA production, and endothelial function, reducing hypertension.[60-64]

Natural Medicines

Natural medicines, including polyphenol-rich foods (green tea, garlic, berries) and herbal remedies (Salvia miltiorrhiza, Panax ginseng), help manage hypertension by promoting beneficial bacteria, SCFA production, and reducing inflammation. Probiotics and prebiotics improve gut barrier function, mitigating LPS-induced vascular dysfunction.[11,54]

CONCLUSION

In conclusion, the gut microbiota is essential for blood pressure regulation through multiple pathways, such as generating short-chain fatty acids and influencing immune system activity, and regulation of neurohumoral pathways. Dysbiosis, often induced by factors such as diet, antibiotics, and lifestyle, can contribute to hypertension by promoting inflammation and endothelial dysfunction. Targeting gut microbiota through interventions in diet, probiotics, and natural medicines holds promise for managing hypertension. However, future research is essential to fully understand the underlying mechanisms and optimize microbiome-based therapies for effective hypertension treatment and prevention.

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