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Gut microbiota in hypertension

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Abstract

Purpose of review—Hypertension, which is present in about one quarter of the world's population, is responsible for about 41% of the number one cause of death, cardiovascular disease. Not included in these statistics is the effect of sodium intake on blood pressure, even though an increase or a marked decrease in sodium intake can increase blood pressure. This review deals with the interaction of gut microbiota and the kidney with genetics and epigenetics in the regulation of blood pressure and salt sensitivity.

Recent findings—The abundance of the gut microbes, *Firmicutes* and *Bacteroidetes*, is associated with increased blood pressure in several models of hypertension, including the spontaneously hypertensive and Dahl salt-sensitive rats. Decreasing gut microbiota by antibiotics can increase or decrease blood pressure that is influenced by genotype. The biological function of probiotics may also be a consequence of epigenetic modification, related, in part, to microRNA. Products of the fermentation of nutrients by gut microbiota can influence blood pressure by regulating expenditure of energy, intestinal metabolism of catecholamines, and gastrointestinal and renal ion transport, and thus, salt sensitivity.

Summary—The beneficial or deleterious effects of gut microbiota on blood pressure is a consequence of several variables, including genetics, epigenetics, lifestyle, and intake of antibiotics. These variables may influence the ultimate level of blood pressure and control of hypertension.

Keywords

microbiota; salt sensitivity; brain gut microbiome axis; gastro-renal axis

Introduction

Blood pressure is distributed continuously from low to high values, but the distribution is skewed to the higher end of the curve (1). There is a direct and quantitative relationship between high blood pressure values and mortality. Hypertension is a major contributor to the number one cause of death, cardiovascular disease (2). The Gaussian distribution and the

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lack of a definable bimodal distribution of blood pressure suggest that blood pressure is regulated by a complex group of interacting genes. The variation of blood pressure is further influenced by the interaction of these genes with epigenetic and environmental factors (3–8). This review deals with the interaction of gut microbiota with genetics and epigenetics in the regulation of blood pressure and salt sensitivity.

Salt sensitivity, defined as >5–10% change in blood pressure in response to a change in NaCl intake, is associated with increased cardiovascular risk, even if the blood pressure does not reach hypertensive levels (9). Mortality and morbidity are both higher in hypertensive subjects and in salt-sensitive normotensive subjects than in salt-resistant normotensive subjects (10–12). About 118 million Americans are afflicted with hypertension and/or salt sensitivity. Fifty to 60 million (≥18 years old) are hypertensive and 58 million are salt-sensitive; 26 million are both salt-sensitive and hypertensive (10, 13). It is recognized that a high sodium diet is deleterious and a low sodium diet has been advocated as part of a healthy life style and treatment of hypertension (2, 12). However, low sodium diet can actually increase blood pressure, i.e., inverse salt sensitivity (13–15), with other adverse consequences (16–18). The mechanisms leading to such adverse consequences and their relationship to “salt-resistant” and “salt-sensitive” genes are not known.

The long-term regulation of blood pressure rests on renal and non-renal mechanisms (19–21). The impaired renal sodium handling in essential hypertension and salt sensitivity are caused by aberrant counter-regulatory natriuretic and antinatriuretic pathways. The nervous system, including renal nerves (22–25) and the parasympathetic and sympathetic nervous systems (26), renin-angiotensin-aldosterone system (24, 25, 27–29), and endothelin via the ET_A receptor (30) are examples of antinatriuretic pathways. An important counter-regulatory natriuretic pathway is afforded by the renal dopaminergic system. Aberrations of this system are involved in the pathogenesis of hypertension (26, 31–35), including that associated with obesity (36–38). However, the gastrointestinal tract has to be integrated in the overall regulation sodium balance and blood pressure because it the first organ exposed to ingested sodium (39, 40). Inhibition of gastrointestinal sodium transport is now being considered in the treatment of essential hypertension (41). Moreover, the gut microbiota can modify the expression of the hypertensive phenotype (42–44).

Gut microbiota and hypertension

The gut microbiota, dominated to a large extent by *Firmicutes* and *Bacteroidetes* and to a lesser extent by *Actinobacteria* and *Proteobacteria* (45), constantly adapt to lifestyle modifications, such as diet (46, 47) and even exercise (48). The gut microbiota can regulate about 10% of the host’s transcriptome, especially those genes related to immunity, cell proliferation, and metabolism (49, 50). The gut microbiota may play a role in the development of cardiovascular disease, including arteriosclerosis and hypertension. Female C57BL/6J *Apoe*$^{-/-}$ mice develop atherosclerosis related to increased trimethylamine N-oxide (TMAO) levels following fecal microbial transplantation from atherosclerosis-prone C57BL/6J mice fed choline diet (51). Toxic metabolites, such as p-cresol, indoxyl sulfate, and TMAO, are produced following fermentation of protein by gut microbiota (52–54). Chronic kidney disease patients have elevated plasma levels of TMAO that are derived from

the metabolism of dietary choline, phosphatidylcholine (lecithin), and l-carnitine by microbiota (55). This elevation in plasma TMAO levels is probably mainly due to gut microbial action, because genes play a minor role in determining TMAO levels in humans (56).

Short chain fatty acids (SCFA) produced by the gut microbiota (40) influence blood pressure that is related to renal sensory nerves (43, 57). These SCFAs activate two orphan G protein-coupled receptors, GPR41 (aka Free Fatty Acid Receptor 3), GPR43 (aka Free Fatty Acid Receptor 2), and olfactory receptor 78 (Olfr78). The increase in blood pressure caused by SCFA-induced renin release from the afferent arteriole is mediated by Olfr78. This, in turn, can be counteracted by the vasodilatory action of GPR43 (43, 57). SCFA, via GPR43, also suppresses insulin signaling in adipocytes, improving metabolism, in part, by inhibiting accumulation of fat in adipose tissue (58). By contrast, GPR41 increases energy expenditure by stimulating the sympathetic nervous system, but this could also lead to an increase blood pressure (59).

Chronic low-grade inflammation can be a cause or consequence of hypertension (60). Low-grade inflammation can be the result of a reduction in microbial gene richness (61). Preeclampsia is associated with hypertension and inflammation, the incidence of which is decreased by chronic intake of probiotics (62). Changes in the ratio of the microbes *Firmicutes* and *Bacteroidete*s have been used as a biomarker for pathological conditions. The *Firmicutes* and *Bacteroidetes* ratio was recently reported to be increased in spontaneously hypertensive rats, angiotensin II- induced hypertension in rats, and small group of humans with essential hypertension. The oral administration of minocycline normalized the *Firmicutes* and *Bacteroidetes* ratio and blood pressure of spontaneously hypertensive rats and rats with angiotensin II- induced hypertension (63). Angiotensin converting enzyme type 2 (ACE2)-mediated regulation of gut microbiota is important in epithelial immunity (64). Lactobacilli also produce biologically active peptides capable of inhibiting ACE1 (65); ACE2-mediated production of angiotensin 1–7 decreases while ACE1-mediated production of angiotensin II increases blood pressure (28).

Consumption of milk fermented with *Lactobacilli* lowered blood pressure in hypertensive humans (66). The antihypertensive effect of blueberries may also be due to *Lactobacilli* in the gut (67). Oral administration of sour milk to spontaneously hypertensive rats has been reported to lower systolic blood pressure. Phenylacetylglutamine is a gut microbial metabolite that is negatively associated with pulse wave velocity and systolic blood pressure (68). A meta-analysis of randomized, controlled trials in humans showed that probiotic consumption modestly decreased both systolic and diastolic blood pressures with a greater effect when at least 10^{11} colony-forming units are taken for at least 8 weeks and if multiple species of probiotics are consumed (69).

The role of a particular species of gut microbiota on blood pressure regulation needs to be sorted. For example, both the Dahl salt-sensitive and salt-resistant rats on a high salt diet have more *Firmicutes* than *Bacteroidetes* but the ratio may be the same in these two Dahl rat strains. This is in contrast to the aforementioned increased *Firmicutes* and *Bacteroidetes* ratio in spontaneously hypertensive rats, angiotensin II- induced hypertension in rats, and

hypertensive humans (63). The amount of *Bacteroidetes*, especially the S24-7 family, and the family *Veillonellaceae* of the *Firmicutes* phylum was higher in Dahl salt-sensitive than Dahl salt-resistant rats. Dahl salt-sensitive rats given cecal content from Dahl salt-resistant rats had higher blood pressure, higher *Veillonellaceae*, higher plasma acetate and heptanoate, lower sodium excretion, and shorter life span that those that received cecal content from Dahl salt-sensitive rats (70). These effects were not found in Dahl salt-sensitive rats fed a low salt diet or antibiotics. By contrast, the blood pressures of Dahl salt-resistant rats on high salt diet were not affected by cecal content from Dahl salt-sensitive or salt-resistant rats. There are also no differences in *Olfr78* and *Gpr41* sequences between these two rat strains (108). However, antibiotic treatment resulting in a reduction in the biomass of the gut microbiota elevated the blood pressure in *Olfr78* knockout but not wild-type mice (43). Thus, the influence of that gut microbiota on blood pressure is modulated by genetics.

Gut microbiota and gastrorenal axis

There are monoamine-containing enterochromaffin cells in the mucosa and submucosa of different portions of the stomach and small intestines (71). The gut microbiota can influence the ability of enterochromaffin cells to produce serotonin, dopamine, and norepinephrine that can influence the behavior of the host, termed brain gut microbiome axis (72, 73) and renal function, termed gastrorenal reflex (74, 75). The absence of gut microbiota has been reported to increase anxiety-like behavior and decreased dopamine turnover in the frontal cortex, hippocampus, and striatum in response to acute stress in rats (76). Norepinephrine, released in response to stress, can also increase the growth and production of virulence-associated factors of gram-negative bacteria. Gut-germ-free stress-sensitive F344 rats had abnormal behavior associated with increased glucocorticoid mRNA, but decreased dopamine turnover in the hippocampus (77). However, in BALB/c salt-resistant mice, the oral administration of antibiotics increased exploratory behavior that was not due to changes in gastrointestinal transmitters, such as serotonin, norepinephrine, and dopamine (78). By contrast, specific-pathogen free mice had increased production of norepinephrine and dopamine in the cecum and colon (79). Dopamine, via D_1-like receptors, can inhibit Na^+, K^+ ATPase activity and electrolyte transport in the jejunum of young but not adult rats (80). In adult rats, D_1-like receptors stimulate potassium secretion in the duodenum (81) and inhibit ileal ion transport (82).

Dietary factors may also influence intestinal L-3,4- dihydroxyphenylalanine (L-DOPA) concentrations, although the effect of gut microbiota in this process is unknown. A two-week intake of a low salt diet was associated with increased dopamine but decreased L-DOPA levels in the jejunal mucosa. By contrast, high salt intake markedly increased the tissue levels of both dopamine and L-DOPA without changes in dopamine/L-DOPA ratios (83). The major mechanism for the increase in renal dopamine production with salt loading has been suggested to be caused by neural L-DOPA spill-over into the circulation (84, 85). Dopamine, produced in the kidney, and not converted to norepinephrine, is responsible for at least 50% of sodium excretion during conditions of moderate sodium excess (32–34). However, gastrin secreted by G-cells in the stomach and duodenum and released into the circulation (39, 86) may aid in this process. Gastrin is taken up by renal cortical tubules to a

greater extent than the other enterokines released after a meal (87). Gastrin then acts on its receptor, the cholecystokinin B receptor expressed in several nephron segments (88) to increase renal dopamine production by increasing the renal tubular uptake of L-DOPA (unpublished data). Gastrin synergistically interacts with renal D_1 receptors to inhibit sodium transport, enabling the excretion of a sodium load (74, 88–90).

Gut microbiota, genetics, hypertension, and salt sensitivity

The gut microbiota is influenced not only by nutrition and environment but also by genetic factors (91, 92). The gut microbiota can modify the expression of the hypertensive phenotype in mice with germ-line deletion of *Slc26a6*, which encodes an anion exchanger, *Olfr78*, which encodes an olfactory receptor, or toll-like receptor 5 (*Tlr5*), a gene component of the innate immune system expressed in the gut mucosa (42–44). Dietary nutrients have also been reported to affect microRNA (miR) and DNA methylation and acetylation and affect blood pressure. The biological function of probiotics has been suggested to be a consequence of epigenetic modification (93).

As aforementioned, the increase in blood pressure with an increase in sodium intake occurs in normotensive as well as hypertensive humans and is predictive of increased cardiovascular events and mortality, irrespective of basal blood pressure levels (10, 11). The mechanisms underlying salt sensitivity are not well understood (94–98). However, genetics can determine the blood pressure response to salt intake (31, 99–105). We have recently reported that intronic variants (intron 22–23 [rs7571842] and intron 25–26 [rs1017783]) of SLC4A5 and GRK4 (GRK4 65R>L rs2960306]) are associated with salt sensitivity in two Euro-American populations (99). GRK4 is important in the regulation of the dopamine receptors and as aforementioned, dopamine receptors are important in the regulation of renal sodium transport and blood pressure (21, 31–38, 105, 106). Human GRK4 65 R>L and two other human GRK4 gene variants (GRK4 142 A>V rs1024323, GRK4 486 A>V rs1801058) constitutively impair dopamine receptor (types 1 and 3) function (105). GRK4 gene variants cause hypertension in transgenic mice (105, 106) and salt sensitivity (unpublished) and thus fulfill the essential test for the demonstration that these genetic variants are causal of a complex trait (107), e.g., hypertension and salt sensitivity.

Gut microbiota, epigenetics, hypertension, and salt sensitivity

Genome-wide association studies (GWAS), which have identified only 2% of the genetic factors believed to influence blood pressure variation (3, 5, 6, 108), did not report *GRK4* or *SLC4A5* to be associated with hypertension. However, the failure to identify *GRK4* and *SLC4A5* in GWAS does not, by itself, eliminate *GRK4* and *SLC4A5* gene variants or any particular gene as causative of hypertension or salt sensitivity (or any phenotype). The current presentation of GWAS data often fails to report all truly associating variants if they do not meet arbitrary P-value cutoffs (5, 109). Moreover, the chips may not contain the gene of interest. For example, *SLC4A5* rs10177833 is not in any of the Affymetrics chips and rs7571842 is found in only 3 of the 6 Affymetrix chips. Illumina chips have both variants only in Human1M-Duo-v3 and each variant in only 1 of 7 chips. Affymetrix chips do not have $GRK4^{142V}$ and the only Affymetrix chip that has $GRK4^{486V}$ is Genomewide 6. The

Illumina chips, except for Illumina Human 1M-Duo-v3, do not have *GRK4*^{486V}; not all the chips have *GRK4*^{65L}. The failure of GWAS to identify the association of *GRK4* or other genes with hypertension in some studies (109–112) may also be due to a failure to examine gene-gene and gene-environment (salt sensitivity) interaction.

The lack of powerful genetic association in essential hypertension, especially salt-sensitive hypertension, as with type 2 diabetes and metabolic syndrome, may indicate the importance of gene modifiers, such as epigenetics, especially resulting from environmental influence (113–115). Diet, including salt and gut microbiota can influence epigenetics (116–119); salt can increase oxidative stress (120, 121) and oxidative stress can influence epigenetics (e.g., histone deacetylase activity) (122). Lysine-specific demethylase 1 regulates histone methylation by demethylating histone H3 at lysine residues 4 and 9 and is involved in salt-sensitive hypertension (7, 8, 114, 118, 123). Certain miRs have been implicated in salt sensitivity and inverse salt sensitivity of blood pressure (114, 124–128). For example, miR-320 and miR-26b are increased in the aorta while miR-21 and miR-1331 are decreased in the aorta and myocardium, respectively, in Dahl salt-sensitive rats fed a high salt diet (125, 126). Several miRs in human renal proximal tubule cells were found to distinguish salt-resistant from salt-sensitive human subjects, including miR-3661, miR-3126, miR-3183, and miR-615-5p while miR-4516 was able to distinguish salt sensitivity from inverse salt sensitivity (127). Mir-124 expression is also increased in urinary exosomes of salt-sensitive subjects (127) and can regulate c-Myc (128, 129). C-Myc, being a proto-oncogene (130, 131), is of interest because there is a positive association of hypertension and cancer, at least in males (132) and increased dietary salt intake increases the risk of gastric cancer (133).

Conclusion

In summary, microbiota can be controlled by many factors including diet, physical activity, genetics, and epigenetics. The influence of gut microbiota on the host may be partially explained by the generation of SCFA, including the beneficial SCFAs (acetate, butyrate, and propionate) and the non-beneficial lactate. These SCFA acting on cell surface receptors, including GPR43, GPR41, and Olfr78 regulate blood pressure (Figure 1). Gut microbiota can also influence the state of immunity and inflammation, cell metabolism, and proliferation that may eventually affect blood pressure.

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Key Points

1. Genome-wide association studies on blood pressure do not take into account the effect of life-style or intake of salt and antibiotics. Salt sensitivity of blood pressure should take into account not only the ability of a high sodium intake to increase blood pressure and a low sodium intake to decrease blood pressure, but also the ability of a marked decrease in sodium intake to increase blood pressure. The intake of antibiotics at the time blood pressure is measured should be taken into account because antibiotics, by altering the gut microbiota, can affect blood pressure.
2. The lack of powerful genetic association in essential hypertension, especially salt-sensitive hypertension, as with type 2 diabetes and metabolic syndrome, suggests the importance of gene modifiers, such as epigenetics, especially resulting from environmental influence. Nutrition, including salt, and gut microbiota can influence epigenetics.
3. Gut microbiota can influence the production of monoamines by enterochromaffin cells. The gut production of serotonin, dopamine, and norepinephrine can affect not only the behavior of the host (brain-gut axis) but also the ability of the kidney to excrete a sodium load (gastro-renal axis).
4. Gut microbiota can regulate genes related to immunity, inflammation, and metabolism. Toxic metabolites produced following fermentation of protein, such as trimethylamine N-oxide, can also lead to chronic renal disease; the latter may be independent of genetic make-up of the host.

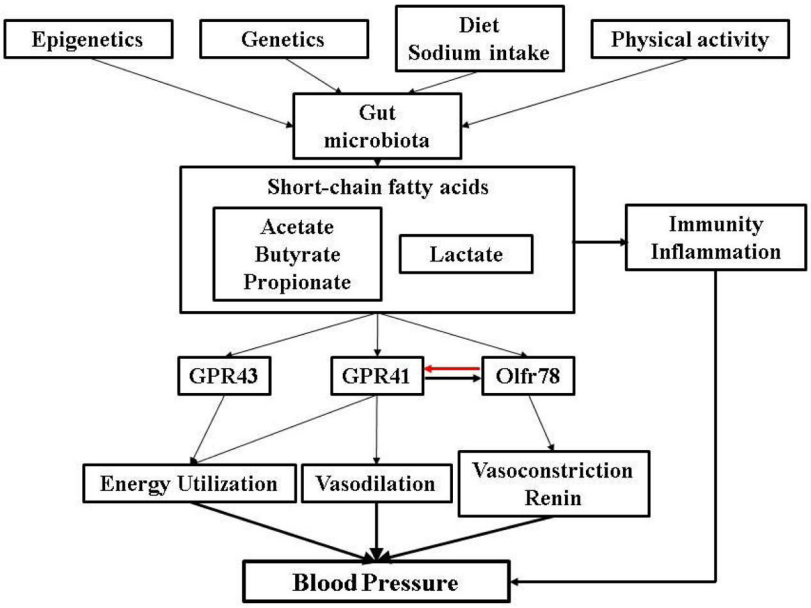

Figure 1.

Microbiota can be controlled by many factors including diet, physical activity, genetics, and epigenetics. The influence of gut microbiota on the host may be partially explained by the generation of short chain fatty acids, including the beneficial acetate, butyrate and propionate, and non-beneficial lactate. These short chain fatty acids acting on cell surface receptors, including GPR43, GPR41, and Olfr78 regulate blood pressure. GPR41 and Olfr78 counter-regulate each other.