REVIEW
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Gut Microbial Metabolites and Blood Pressure Regulation: Focus on SCFAs and TMAO

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Shifts in the gut microbiome play a key role in blood pressure regulation, and changes in the production of gut microbial metabolites are likely to be a key mechanism. Known gut microbial metabolites include short-chain fatty acids, which can signal via G-protein-coupled receptors, and trimethylamine-N oxide. In this review, we provide an overview of gut microbial metabolites documented thus far to play a role in blood pressure regulation.

blood pressure; G-protein-coupled receptors; gut microbial metabolite; hypertension

Introduction

It is now well-appreciated that the gut microbiota has the ability to influence the physiology of the host organism (6, 9, 19, 61, 71, 81). One way that this is accomplished is via metabolites produced by the gut microbiota, which can be absorbed into the blood stream of the host and thus can influence host proteins at distant sites. Recently, multiple studies have outlined connections between changes in gut microbial metabolites and hypertension. Hypertension is correlated with shifts in the gut microbiota (known as gut dysbiosis) in humans (59, 93, 116) and in animal models (3, 28, 64, 66, 101, 116). As a consequence, microbial metabolite production is altered in hypertension (21). Different gut microbial metabolites have been reported to have both positive (35, 69) and negative (55, 59, 105, 118) effects on cardiovascular function. In this review we will discuss current knowledge regarding specific gut microbial metabolites, which are reported to influence blood pressure regulation.

Short-Chain Fatty Acid Metabolites

Among the more studied species of gut microbial metabolites are short-chain fatty acids (SCFAs), and thus SCFAs will be a primary focus of this review. The term "SCFAs" refers primarily to straight-chain 2–4 carbon compounds: acetate, propionate, and butyrate. SCFAs are byproducts of dietary fiber digestion by the gut microbiota in the colon and cecum. Gut microbial production of SCFAs is quite robust; the concentration of SCFAs in the colonic lumen has been reported to be ~100 mM (18).

SCFAs are absorbed into the bloodstream of the host by diffusion as well as by monocarboxylate transporters (23). Although the host can produce SCFAs, the vast majority of circulating SCFAs are microbial in origin. This is evidenced by the fact that SCFAs are virtually undetectable in the plasma of germ-free mice (which lack gut microbiota) (78). Acetate is the most abundant of the SCFAs in the circulation, generally reported to be at least 100 μM. However, acetate levels can be much higher with different diets, and the exact proportion of acetate:propionate:butyrate also varies depending on dietary manipulations (31, 58). However, acetate is consistently the most abundant of the three SCFAs, both in colonic lumen and in circulation (25, 31, 58, 96).

SCFA-Mediated Cell Signaling: G-Protein-Coupled Receptors

SCFAs in circulation can affect host physiology in a number of ways, including by acting as ligands for G-protein-coupled receptors (GPCRs). Here, we will briefly discuss each of the GPCRs that are known to be activated by SCFAs: Gpr41, Gpr43, Gpr109a, Olfr78, and Olfr558. The relevant sites of expression, ligands, and mechanism (if known) are summarized in FIGURE 1.

Gpr41 (free fatty acid receptor 3) and Gpr43 (free fatty acid receptor 2) were first reported as SCFA receptors in 2003 by two separate groups (15, 56). Gpr43 couples to both G_i and G_q proteins, whereas Gpr41 couples to G_i (15, 56). However, for both Gpr41 and Gpr43, activation has been reported to lead to both inhibition of cAMP and increases in intracellular calcium (56). Both Gpr41 and Gpr43 are activated by three to six ligands, depending on the assay used. Propionate is the best ligand for both receptors, with acetate, butyrate, and isobutyrate also being relatively strong ligands. Although

the exact EC_{50} values reported vary, Gpr41 and Gpr43 are activated by SCFAs in the μM range. In addition to SCFA ligands, β-hydroxybutyrate has been reported to be both an agonist (111) and an antagonist (54) for Gpr41. With regard to blood pressure regulation, Gpr41 is known to be expressed in the vascular endothelium (69) and in the autonomic ganglia (54, 73), where activation promotes ERK1/2 phosphorylation (54). Gpr43 is also expressed in blood vessels (although the cell type of expression has not yet been reported) (79). Gpr41 KO mice have isolated systolic hypertension, implying that Gpr41 plays an important role in setting basal vascular tone (69). This is consistent with the fact that acute delivery of SCFAs causes vasodilation ex vivo (69) and that acute delivery of SCFAs also causes a brief hypotensive response in vivo (79). Although the hypotensive response to SCFAs is not absent in Gpr41 KO mice, the dose response is shifted (79). This implies that Gpr41 is not the sole player in SCFA-mediated changes in vascular tone. Further studies are needed to elucidate the role of SCFAs in this context.

Gpr109A is a SCFA receptor that is activated by butyrate (EC_{50} ~1 mM) but not by acetate or propionate (94). Gpr109A is also a receptor for β-D-hydroxybutyrate and for niacin (94, 97, 110). Gpr109A signaling leads to G_i activation and thus to decreases in intracellular cAMP (91). With regard to blood pressure regulation, Gpr109A is expressed in the rostral ventrolateral medulla (RVLM), where it plays a role in the central control of blood pressure in response to activation by niacin, which leads to an increase in L-glutamate and ROS production (80); to our knowledge, however,

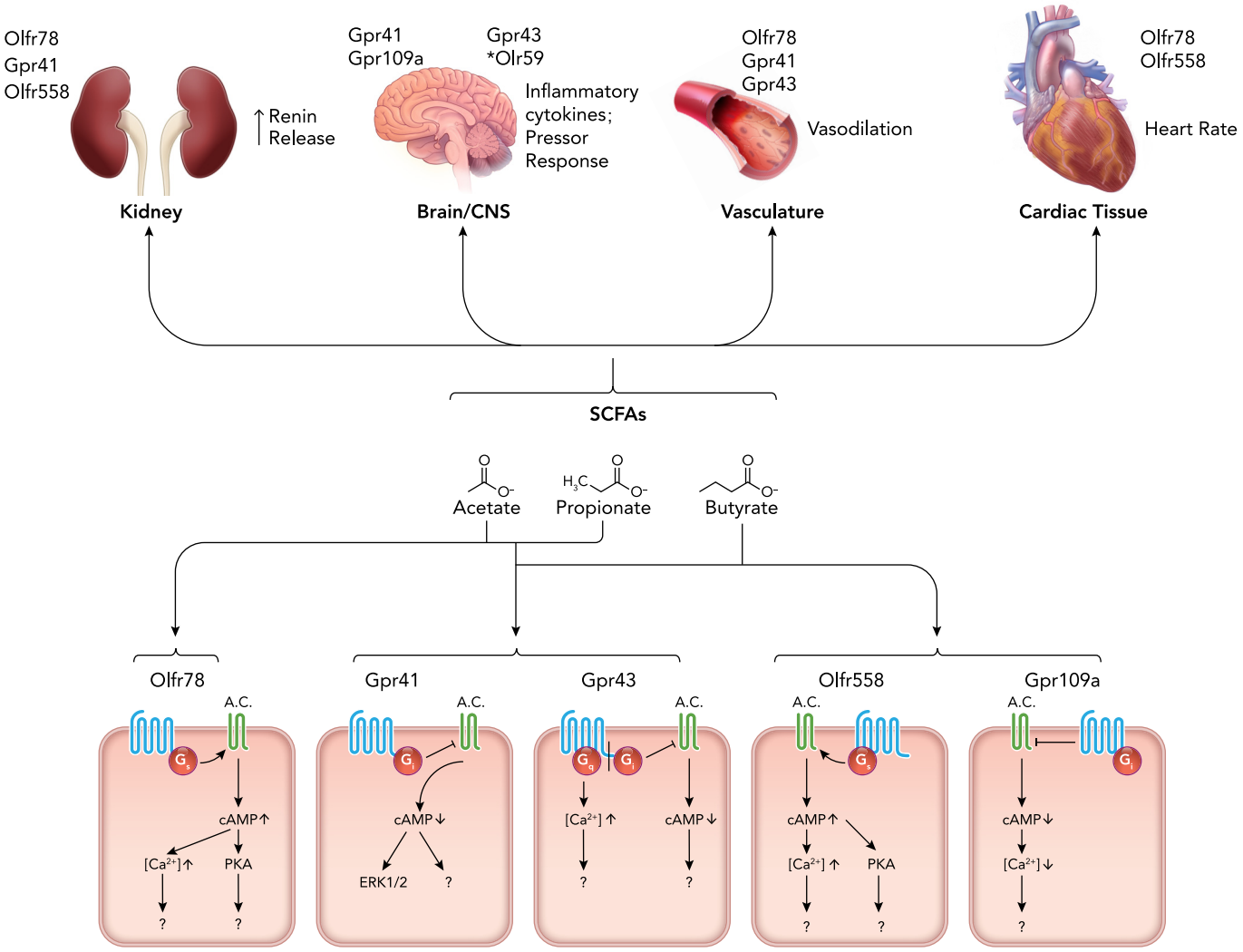

FIGURE 1. **Mechanisms and sites of microbial SCFA-mediated blood pressure regulation**
Production of short-chain fatty acids (SCFAs) in the gut leads to absorption in the distal gut through diffusion and active transport. SCFAs then travel through the circulation to activate receptors in the kidney, brain, sympathetic nervous system, vasculature, and heart, leading to blood pressure effects. (*Note: Olr59 is the rat ortholog of Olfr78.) Although each organ system shows known receptor expression, these effects have not all been proven to be due to receptor activation. Acetate, propionate, and butyrate are all ligands for Gpr41 and Gpr43, whereas acetate and propionate activate Olfr78. Butyrate acts on Olfr558 and Gpr109a. Niacin can also activate GPR109a. Activation of these GPCRs leads to downstream effects that are yet to be elucidated.

the role of Gpr109a in blood pressure regulation has not been tied to butyrate.

Olfr78 and Olfr558 are both olfactory receptors, and both are well-known to be expressed in numerous tissues other than the nose where they act as chemosensory GPCRs for SCFAs (26, 37). Of note, in this review, we will primarily use the murine nomenclature for these receptors (Olfr78 and Olfr558), but the human orthologs of Olfr78 and Olfr558 utilize a different nomenclature (OR51E2 and OR51E1), and the rat orthologs have yet a different nomenclature (Olr59 and Olr63). As olfactory receptors, both Olfr78 and Olfr558 are thought to signal by increasing cAMP (in the olfactory epithelium, this occurs via coupling to G_{olf}; presumably, these receptors can also couple via G_s).

Olfr78 was initially deorphanized in 2009 by two groups: one group found that the human ortholog, OR51E2, responded to propionate (82), whereas the other group reported that OR51E2 was activated by β-ionone (70). A third group in 2013 reported that both Olfr78 and OR51E2 were activated by acetate/acetic acid and propionate/propionic acid, but not by butyrate/butyric acid or β-ionone (79). However, it is worth noting that β-ionone activation of OR51E2 has been consistently reported by others (43, 70). β-Ionone activation is typically reported by studies utilizing a calcium signaling readout for Olfr78 activation, whereas the study that failed to see β-ionone activation used a cAMP assay; thus it is possible that β-ionone is an example of biased agonism. OR51E2 has also been reported to respond to androstenone derivatives (1, 70). In 2015, it was reported that Olfr78 was activated by acetate, propionate, and lactate (20). However, a separate report in 2016 failed to see lactate activation for OR51E2 (4), and two studies reported Olfr78 activation by lactate only at very high levels (4, 117). For SCFA activation of Olfr78, EC_{50}s are in the low millimolar range. Finally, a report in 2020 identified the corresponding esters of acetate and propionate as Olfr78 ligands by screening for activation in the olfactory epithelium in situ (90). Intriguingly, these authors suggest that the esters may not be ligands themselves but may be converted into their corresponding acids by enzymes in the nasal mucus.

With regard to blood pressure regulation, Olfr78 is expressed in blood vessels (smooth muscle cells), as well as in the renal afferent arteriole (79), where it has been shown to impact renin release (79). Specifically, it was shown that isolated juxtaglomerular apparati from wild-type mice release renin in response to a SCFA but that this response is markedly attenuated in juxtaglomerular apparati from Olfr78 KO mice (79). In agreement with this, it was also reported that Olfr78 KO mice have lower circulating plasma renin (79). As for the role of Olfr78 in vascular smooth muscle, the acute hypotensive response to SCFAs is not absent in Olfr78 KO mice, but (like in Gpr41 KO mice) the dose-response is shifted (79).

Olfr558, the most closely related olfactory receptor to Olfr78, has been reported to respond to butyric acid/butyrate (2, 46). One group has also reported that Olfr558 can respond to nonanoic acid (82), although other groups have not seen activation with this compound (45, 46). A study in 2019 identified a total of 18 ligands for Olfr558 and OR51E1, with butyrate acting as the strongest activator of downstream signaling (cAMP) for both the murine and human ortholog (EC_{50} of ~0.5 mM) (46). Although a role for Olfr558 in blood pressure regulation has not been investigated, Olfr558 is expressed in the renal cortex (46), and OR51E1 is expressed in the heart (50). A microarray study has also identified Olfr558 expression in isolated juxtaglomerular cells (16).

Finally, it is important to note that GPCR-mediated SCFA signaling has been well-conserved evolutionarily, with orthologs in different species responding similarly for Gpr41 (15), Olfr78 (79), and Olfr558 (46). In fact, although many murine olfactory receptors do not have clear orthologs in other species, both Olfr78 and Olfr558 are extremely well-conserved among placental mammals, having complete one-to-one orthologous relationships among at least 13 different species (72).

SCFA-Mediated Cell Signaling: Other Pathways

In addition to GPCR signaling, SCFAs can also affect cell biology by affecting cell proliferation. SCFAs have been reported to both increase (34, 84) and decrease (4, 14, 34, 38, 52, 87) cell proliferation. It has been suggested that butyrate stimulates the growth of colonocytes in the absence of the Warburg effect but inhibits proliferation when the Warburg effect is in play (34). SCFAs also have effects on apoptosis (5, 22, 39) and on histone deacetylases (HDACs) (24, 30, 47, 65, 99). These effects on cell proliferation, apoptosis, and HDACs are generally thought to be independent of GPCRs, although Gpr41 has been suggested to play a role in mediating HDAC inhibition (112). Although these pathways are no doubt important, they have not as of yet been implicated in blood pressure regulation and thus will not be a focus of this review.

The Microbiota, SCFAs, and Blood Pressure Regulation

The interplay between gut microbial metabolites and blood pressure regulation has been estab-

lished in animal models (11, 64, 69, 75, 79, 95). In studies involving mice and rats, fecal microbiota transplantation (FMT) into germ-free mice has become the gold standard for definitively identifying key roles of the microbiome in disease states such as obesity, irritable bowel disorders, and hypertension (29, 44, 53, 66, 81). As the name implies, FMT involves the transplantation of fecal microbiome samples from a donor into the intestinal tract of a recipient. Using FMT, multiple studies have linked gut dysbiosis and shifts in SCFA-producing bacteria with hypertension in both human patients and animal hypertension models (3, 59, 66, 116). Mell et al. performed FMT after antibiotic treatment and found that blood pressure increased in salt-sensitive hypertensive Dahl rats that received FMT from salt-resistant Dahl rats (66). This hypertensive phenotype was correlated with higher levels of plasma acetate (66). Allelic variations were found in olfactory receptor genes between the salt-sensitive and salt-resistant Dahl rat strains, suggesting a potential mechanism for the difference in hypertensive response (66). However, this study did not look at levels of other SCFAs such as propionate or butyrate. These results are corroborated in another study in Dahl salt-sensitive rats that found that CRISPR excision of G-protein-coupled estrogen receptor 1 (*Gper1*) resulted in lower blood pressure, and FMT with microbiota from WT hypertensive counterparts reversed the protective blood pressure effect of Gper1 KO and increased plasma acetate levels (101). High-salt-diet-induced hypertension in salt-sensitive rats also increased fecal acetate and propionate levels in correlation with increased blood pressure (13). Another study in spontaneously hypertensive rats (SHR) also showed increased cecal butyrate levels at baseline compared with normotensive WKY controls, with a corresponding decrease in circulating butyrate, indicating a possible defect in SCFA transport and absorption in this context (114).

Despite these studies, there is conflicting evidence as to whether increased SCFAs positively or negatively correlate with hypertension (3, 116). A study by Yang et al. found that hypertensive rats had a significantly decreased population of acetate and butyrate-producing bacteria compared with their normotensive Wistar Kyoto counterparts (116). This is corroborated by Adnan et al., who also saw a decrease in butyrate-producing bacteria in a similar hypertensive rat model (3); both of these studies were done in a SHR model. Yang et al. performed similar studies in an angiotensin II (Ang II) rat model of hypertension and demonstrated that Ang II-induced hypertension led to similar reductions in bacterial diversity (116). Notably, a study from Karbach et al. showed that germ-free mice are resistant to Ang II-induced hypertension, demonstrating a pivotal role of the microbiota in this model of hypertension (51). This finding is especially impactful given that Ang II infusion is the most common animal hypertension model used in NIH-sponsored studies (40). Finally, a key study by Li et al. performed FMT into a germ-free mouse model and found that blood pressure increased in mice that received FMT from hypertensive human donors (59). This finding demonstrated that a hypertensive phenotype arises from a particular gut microbial composition and that the phenotype can be transferred via the microbiota (59). Although correlative links between gut dysbiosis and changes in SCFA levels have been established by these studies, they do not establish that these effects are mediated by direct effects of SCFAs on blood pressure regulation and/or hypertension. It is also worth noting that the correlation between gut microbiota and blood pressure regulation appears to be bidirectional—there is clear evidence both that the gut microbiota are remodeled by hypertension and that altering the gut microbiota can alter blood pressure regulation.

Effects of SCFA Supplementation at Baseline and in Hypertensive Models

Before we consider the effects of direct SCFA supplementation on models of hypertension, it is important to briefly touch on what is known about the interplay between SCFAs and blood pressure in normal physiology. Studies suggesting that SCFAs can cause hypotensive effects have existed for decades (12, 27, 67, 69, 74). Direct application of SCFAs have been shown to cause vasorelaxation in mouse, rat, and human isolated vascular tissue ex vivo (27, 67, 69, 74). SCFAs are also known to acutely reduce blood pressure when delivered as a bolus intravenously, intraperitoneally, or intracolonically (75, 79, 86). A recent study implied that central nervous system activation may play a role, since intracerebroventricular injection of butyrate led to not only a decrease in mean arterial pressure but also activation of cardioregulatory brain regions (114). This activation was attenuated in a SHR model. This study also showed decreased expression of Gpr41 and Olr59 (the rat ortholog of Olfr78) in the hypothalamus of the rat, hinting at a potential mechanism (114). In separate studies, acute delivery of SCFAs has also been shown to increase heart rate when given intraperitoneally (54), but, when administered intracolonically, another study showed heart rate decreased (75).

Given the observation of dysbiosis-dependent changes of SCFAs in hypertension, several studies have directly manipulated SCFAs via supplementation in animal hypertension models. A study from

Wang et al. found that intramedullary butyrate infusion in Ang II-treated rats reduced blood pressure and urinary excretion of renin and markers of renin angiotensin aldosterone system (RAAS) activation (59). Butyrate treatment of astrocytes isolated from a SHR model also showed differential regulation of bioenergetics and neuroinflammatory genes compared with normotensive astrocytes (115). Another study using telemetry-implanted mice showed butyrate supplementation via IP injection reduced Ang II-induced hypertension, improved gut barrier function, and restored gut barrier hypoxia (103). Marques et al. found that acetate supplementation in drinking water of deoxycorticosterone acetate (DOCA)-salt hypertensive mice also showed reduction in systolic and diastolic pressures, fibrosis, and hypertrophy (64). Recently, a study from Bartolomeus et al. found that propionate supplementation in drinking water attenuated hypertension, cardiac hypertrophy, and fibrosis in the Ang II hypertension mouse model (11). These cardioprotective effects were abrogated in regulatory T-cell-depleted Ang II mice, suggesting that propionate acts through regulatory T-cells (11). Although the effects of SCFA supplementation in animal models of hypertension are extremely promising, it remains to be seen whether it would be effective in treating human models of hypertension.

Clinical Data

Confirming established animal model findings in clinical research remains a significant hurdle in elucidating the role of SCFAs in hypertensive settings. However, some clues can be gleaned from clinical studies from the past few years. Two clinical studies looking at hypertensive and pre-hypertensive patients both found significantly decreased microbial diversity and levels of SCFA-producing bacteria compared with healthy patients by fecal metabolite analysis (59, 113). A separate study conducted by Gomez-Arango et al. reported that butyrate production was negatively associated with blood pressure in a clinical study of pregnancy-induced hypertension (including gestational hypertension, preeclampsia, and HELLP syndrome) (44). In obese pregnant women, elevated systolic and diastolic blood pressure correlated with a decrease in butyrate-producing bacteria and bacterial expression of the butyrate-producing *buk* enzyme (44). In contrast, two clinical studies from de la Cuesta-Zuluaga et al. and Huart et al. demonstrated a correlation between increased fecal levels of SCFAs (acetate, propionate, and butyrate) and hypertension (28, 48). Higher levels of fecal SCFAs could correlate with lower circulating SCFAs due to a defect in transport or absorption, as has been suggested in animal models (114). None of these studies directly looked at circulating SCFA levels; however, a clinical cohort in a study from Kim et al. confirmed that hypertensive human patients showed distinct microbiome composition and that higher blood pressure levels observed in these patients correlated with lower plasma butyrate levels (53).

Although these clinical data primarily show a correlative effect of gut dysbiosis, further clinical studies are currently recruiting or in progress to further evaluate the role of the microbiome in hypertension. Additionally there are a host of variables that can complicate interpretation of clinical data, such as medication, diet (100), age (17), gender (63), and racial background (102). Our knowledge of the impact of these variables on microbiome composition under normal and dysbiosis conditions is still limited. For example, a study by Walejko et al. (102) showed distinct gut microbiota taxonomy and serum metabolite profiles between hypertensive and normotensive white or African-American patients (102). Although this study was a small sample size and did not measure acetate, propionate, or butyrate, it highlights the need for a fuller understanding of racial differences in the development of microbiome-based therapies for hypertension.

Hypertension Origins/Mechanisms

Obstructive sleep apnea (OSA) is significantly more prevalent in hypertensive patients and even more widespread in drug-resistant hypertension (60, 76, 88). Accordingly, multiple animal studies have linked gut dysbiosis to both sleep apnea and hypertension (3, 41). Durgan et al. performed FMT from OSA rats into normotensive rats, which resulted in increased blood pressure levels and lowered levels of butyrate-producing bacteria (3). Ganesh et al. used a rat model of OSA to demonstrate that gut dysbiosis can cause hypertension. Analysis of the gut microbiome in these OSA mice revealed a decrease in SCFA-producing bacteria and a corresponding decrease in plasma acetate (41).

Another potential mechanism of hypertension induction includes overactivation of the gut-brain-microbiome axis. Overactivation of the sympathetic nervous system and adrenergic receptor signaling has been linked to hypertension (62, 85) and gut dysbiosis (83). A study from Toral et al. showed decreased blood pressure and noradrenaline levels on FMT between normotensive and spontaneously hypertensive rats (95). Additionally, FMT induced changes in expression of SCFA receptors Olr59, Gpr41, and Gpr43 in the paraventricular nucleus of the brain, suggesting a possible mechanism (95). In a separate study, Bartley et al.

showed an increase in colonic concentrations of SCFAs in β_1- and β_2-adrenergic receptor knockout mice. SCFAs also have been shown to induce parasympathetic vagal outflow (78) and sympathetic tone (54). These studies highlight the potential interplay between the gut microbiome and the CNS, and provide a potential mechanism for SCFA-mediated hypertension effects.

TMAO/TMA Biosynthesis and Clinical Significance

In addition to SCFAs, another gut microbial metabolite that has been linked to cardiovascular disease is trimethylamine-N oxide (TMAO) (21). However, it is to be noted that the influence of this metabolite is studied more in the context of atherosclerosis rather than on blood pressure regulation. TMAO is a small organic compound that is formed in the liver by the oxidation of trimethylamine (TMA). TMA is produced by gut microbiota from dietary components, including carnitine and choline, which are highly abundant in red meat, fish, and eggs (36). The plasma concentration of TMAO in healthy individuals was measured as 3 μM (92). TMA and TMAO accumulate in plasma under pathophysiological conditions such as end-stage renal disease and chronic kidney disease (10, 92). In healthy individuals, about half of the TMA and TMAO is excreted unchanged from the circulation within 24 h, primarily via urine, respiration, and sweat (7, 8, 89). The remaining half of TMAO reduces back into TMA via the action of TMAO reductase in human gut (36).

Recent studies in animals and humans have elucidated a role for TMAO in metabolic (42), cerebrovascular (118), and cardiovascular (106) diseases. In particular, as noted above, TMAO has been implicated in atherosclerosis (55). Wang et al. have shown a relationship between gut microbial-dependent metabolism of choline and atherosclerosis in an apolipoprotein e knockout ($Apoe^{-/-}$) mouse model (105). Moreover, TMAO levels predict risk for cardiovascular disease in a clinical cohort (105). Another recent study demonstrated that TMAO induced alterations in bile acid profiles and that this led to an increased rate of atherosclerotic lesion formation in the $Apoe^{-/-}$ mouse model (32). Mechanistically, it was suggested that changes in bile acids may lead to activation of farnesoid X receptor and small heterodimer partner (32). Ultimately, this would inhibit bile acid synthesis by reducing *Cyp7a1* expression (32).

A recent dietary intervention study with a crossover design recruited both omnivorous and vegan/vegetarian human subjects and examined changes in TMAO in response to red meat, white meat, or non-meat protein sources. The study showed that chronic red meat consumption increases systemic TMAO by both increasing dietary precursors and increasing TMA/TMAO production from carnitine, as well as reduced renal excretion (104). Increased TMAO has been reported to correlate with poor outcomes, including mortality and cardiovascular disease events, in individuals with Type 1 diabetes (109), and TMAO levels are increased in women with preeclampsia (108). Indeed, there is also evidence in animal models that TMAO can worsen existing disease: TMAO infusion in rats prolongs hypertension in a low-dose Ang II model but did not alter blood pressure in normotensive rats (98).

Other Metabolites

Although the gut microbial metabolites reviewed above are relatively well-studied in terms of blood pressure control, it is likely that there are many other metabolites that may also play a role. For example, gut microbial fermentation also produces gaseous compounds such as hydrogen sulfide (H_2S) and methane (CH_4) (68). In fact, gut microbial production gives rise to ~50% of total circulating and fecal H_2S, and H_2S is a known vasodilator (33, 49, 77, 107). In a recent metabolomics study (21), untargeted metabolomics were used to compare conventional (with gut microbiota) or germ-free mice (without gut microbiota) receiving infusions of either saline or Ang II. In conventional animals, there were 12 plasma metabolites and 96 fecal metabolites, which were significantly different in Ang II-treated mice compared with saline-treated mice. Surprisingly, none of these metabolites were similarly altered in germ-free mice treated with Ang II, implying that the majority of the metabolomic changes that occur in this model are dependent on the gut microbiota. Further studies are required to determine whether these metabolites play direct roles in the presentation of hypertension, and what mechanisms may be involved.

Gaps in the Knowledge

Recent advances showing the wide-ranging effects of microbial metabolites on blood pressure regulation are intriguing, although many mechanistic questions remain to be answered. For instance, SCFA receptors such as Gpr41, Gpr43, and Gpr109a have been found to be expressed in the CNS (54, 80, 95), and there are links between gut dysbiosis and increased sympathetic drive (83), but to date the precise mechanism of the cross talk between gut and CNS remains an open question. Another key pathway, the RAAS and in particular renin release, is also known to be impacted by metabolites via Olfr78 in juxtaglomerular cells (79), but other

downstream effects on the RAAS have not been determined. However, it is also known that SCFA supplementation leads to a decrease in blood pressure and vasodilation (75, 79, 114). Differing levels of GPCR expression across tissues as well as disparate EC_{50} of GPCRs for SCFAs (15, 79) could be a potential explanation, but further studies are required to rectify apparently conflicting physiological effects of SCFAs and other metabolites. Studies including tissue-specific GPCR knockouts and germ-free mouse models will be informative in providing a definitive link between activation of these receptors and microbial metabolite effects on RAAS, CNS, and other novel pathways. Finally, the role of microbial metabolites in other systems that impact blood pressure and hypertension, such as the heart and vasculature, have been hinted at but are yet to be fully explored.

Conclusions

Numerous studies have provided evidence that the gut microbiota and hypertension are linked. However, the nature of this link remains uncertain, since there is clear evidence not only for gut microbes to influence the progression of hypertension but for hypertension to remodel the gut microbiota. We hypothesize that this truly is a bidirectional interaction—for example, hypertension itself may induce changes in gut microbiota, and these changes may then serve to further drive the hypertension. Studies to date have outlined potential mechanistic roles for SCFAs in mediating host-microbe communication in hypertension, often acting via host SCFA G-protein-coupled receptors. Similarly, there are clear roles for TMAO in cardiovascular diseases. However, it seems highly unlikely that SCFAs and TMAO are the only players in mediating communication between microbes and host in the context of blood pressure regulation. Looking forward, in future studies it will be critical to better understand the players involved and to uncover the mechanisms underlying host-microbe communications. This will require not only a more nuanced understanding of SCFA signaling but moving beyond SCFA signaling to understand how other microbial metabolites influence the host and to understand how changes in host physiology result in remodeling of the gut microbiota. ■

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