Role of the microbiota in hypertension and antihypertensive drug metabolism

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Abstract

Recent evidence suggests that the gut microbiota plays an important role in the development and pathogenesis of hypertension. Dysbiosis, an imbalance in the composition and function of the gut microbiota, was shown to be associated with hypertension in both animal models and humans. In this review, we provide insights into host-microbiota interactions and summarize the evidence supporting the importance of the microbiota in blood pressure regulation. Metabolites produced by the gut microbiota, especially short-chain fatty acids, modulate blood pressure and vascular responses. Harmful gut-derived metabolites, such as trimethylamine *N*-oxide and several uremic toxins, exert proatherosclerotic, prothrombotic, and proinflammatory effects. High salt intake alters the composition of the microbiota, and this microbial alteration contributes to the pathogenesis of salt-sensitive hypertension. In addition, the microbiota may impact the metabolism of drugs and steroid hormones in the host. The drug-metabolizing activities of the microbiota affect the pharmacokinetic parameters of antihypertensive drugs and contribute to the pathogenesis of licorice-induced pseudohyperaldosteronism. Furthermore, the oral microbiota plays a role in blood pressure regulation by producing nitric oxide, which lowers blood pressure via its vasodilatory effects. Thus, antihypertensive intervention strategies targeting the microbiota, such as the use of prebiotics, probiotics, and postbiotics (e.g., short-chain fatty acids), are considered new therapeutic options for the treatment of hypertension.

1. Introduction

Recent advances in high-throughput sequencing technology and metabolomics have provided strong evidence for the relationship between the microbiota and hypertension and cardiovascular disease (1-3). The human body is colonized by trillions of microbes, which are collectively referred to as the “microbiota.” The gut microbiota is a highly dynamic organ mediating numerous physiological functions, such as harvesting energy from food, priming the immune system, and producing vitamins and a range of bioactive metabolites. Under physiological conditions, there is a symbiotic balance between the gut microbiota and the host. The disruption of this balance, known as dysbiosis, has been implicated in a variety of pathological conditions, including hypertension (4). In addition, the microbiota is involved in the metabolism of steroid hormones and antihypertensive drugs (5, 6). Therefore, an improved understanding of the host-microbiota relationship may uncover new opportunities for the development of antihypertensive treatment strategies (7). In this review, we highlight the role of the gut microbiota in blood pressure (BP) regulation.

2. Dysbiosis and hypertension

Evidence for the association between dysbiosis and hypertension comes from both animal and human studies (8). Numerous observational studies have shown that a greater proportion of hypertensive animals and humans demonstrate dysbiosis (reduced microbial abundance, richness, and diversity) than their normotensive counterparts (9, 10). Alterations in gut microbiota composition in hypertensive animals/individuals have been reviewed in other articles (11, 12). In both animal and human studies, hypertensive and normotensive groups showed differences with regard to several bacterial taxa. For example, rat models of hypertension showed a reduction in the proportion of *Bacteroidetes* and an increase in *Firmicutes* (13). The large cohort study Coronary Artery Risk Development in Young Adults (CARDIA; n = 529) revealed that gut microbial diversity and *Robinsoniella* abundance were inversely associated with both hypertension and systolic BP (8). The Healthy Life in an Urban Setting (HELIUS; n = 4672) study identified the taxa *Roseburia* spp., *Clostridium* spp. *Romboutsia* spp., and *Ruminococcaceae* spp. as the best predictors of systolic BP (14). This study also revealed that the gut microbiota explained 4.4% and 4.3% of the variance in systolic and diastolic BP, respectively. In the FINRISK 2002 study (n = 6953), 45 microbial genera, of which 27 belong to the phylum *Firmicutes*, and 19 *Lactobacillus* species were associated with BP (15).

3. BP regulation by the microbiota

Evidence from observational studies has not clarified whether gut dysbiosis is a cause or a consequence of hypertension or even a coincident observation. However, studies on germ-free mice bred in sterile isolators who do not have any microbiota support the role of the gut microbiota in hypertension. Germ-free mice infused with angiotensin II (Ang II) had lower BP than conventional mice (16). In another study, germ-free rats showed relative hypotension accompanied by a marked reduction in vascular contractility, with a decrease in arterial actin polymerization. Hypotension and vascular contractility were restored by the introduction of microorganisms to germ-free rats (17). Another study showed that germ-free mice who received a fecal microbial transplant (FMT) from hypertensive human donors developed a similar gut microbiota to their donor, as well as elevated BP (18). Similarly, a FMT from hypertensive rats resulted in BP elevation in normotensive rats (19, 20). These findings demonstrate the direct influence of the gut microbiota on the development of hypertension.

4. Microbiota-derived metabolites and hypertension

The gut microbiota produces a variety of metabolites with important effects on circulating metabolites in the host (**Table 1**) (21). Microbiota-derived metabolites can mediate host receptor activation, signaling, and immunomodulatory effects. Several of these metabolites have been linked to BP regulation, renal sodium regulation, and atherosclerosis (12). Beneficial metabolites produced by the microbiota include short-chain fatty acids (SCFAs) and vitamins. However, the gut microbiota also produces metabolites that are harmful to the host, such as trimethylamine *N*-oxide (TMAO), lipopolysaccharide, uremic toxins, and secondary bile acids (22-24). The effects of the gut microbiota on circulating metabolites in hypertension were studied in germ-free and conventional mice with Ang-II-induced hypertension (25). Unbiased metabolomics revealed that three plasma metabolites (4-ethylphenyl sulfate, *p*-cresol sulfate, and *p*-cresol glucuronide) were upregulated by a 4-week Ang II infusion in conventional mice, although these metabolites were nearly undetectable in germ-free mice. This result implied that the pathological state of hypertension caused dysbiosis, which could be associated with the plasma levels of several microbiota-derived metabolites. However, despite numerous studies showing the relationship between hypertension and dysbiosis, the mechanism underlying hypertension-mediated dysbiosis has not yet been revealed.

4-1. SCFAs

SCFAs are metabolites generated by the gut microbiota as byproducts of the bacterial fermentation of dietary fiber, such as resistant starches. These metabolites may regulate BP through anti-inflammatory and vasorelaxant effects (26). Three SCFAs (acetate, propionate, and butyrate) account for 80% of the total SCFAs produced (27). Although their primary site of action is the intestine itself, SCFAs can be absorbed via the intestinal walls and the portal vein to reach the systemic circulation (3). SCFAs have emerged as potential regulators of BP, and treatment with SCFAs may be beneficial in BP reduction.

SCFAs can bind to and activate the host G-protein-coupled receptors Gpr41, Gpr43, Gpr109a, Olfr558, and Olfr78 in mice (26, 28). GPR41 is expressed in the vasculature and kidneys and is involved in the regulation of vasoreactivity in response to SCFAs (29). The administration of acetate reduced blood pressure. Propionate also induced an acute hypotensive response in mice, which was mediated by Gpr41 (29). Nonetheless, propionate increased the release of renin from juxtaglomerular cells in the kidney through Olfr78 activation (29), suggesting that propionate carries out opposing actions for blood pressure regulation. Various studies have suggested that SCFA treatment lowers BP (30). Propionate administered in drinking water reduced BP and cardiac damage in Ang-II-infused hypertensive mice (31). Butyrate infusion also attenuated Ang-II-induced hypertension in mice by shifting the microbial profile and improving cardiac and vascular function (32). In a deoxycorticosterone acetate-salt hypertensive mouse model, acetate and butyrate intake reduced BP and increased the relative abundance of SCFA-producing gut bacteria (33, 34).

The intake of fermentable dietary fiber, such as resistant starches, provides a substrate for the gut microbiota to produce SCFAs and consequently increases the production of SCFAs and the abundance of saccharolytic bacteria producing SCFAs. A number of experimental and clinical studies have shown the beneficial effect of dietary fiber in protecting against hypertensive organ damage (35). For example, a high-fiber diet reduced BP and cardiac fibrosis in mineralocorticoid excess-treated hypertensive mice (33). A meta-analysis of randomized controlled clinical trials showed that an increase in the intake of dietary fiber reduced BP in patients with hypertension (36). In contrast, the consumption of a low-fiber diet predisposed mice to hypertension, and the addition of SCFAs to a low-fiber diet lowered BP in Ang-II-induced hypertensive mice (37). In clinical studies, hypertensive individuals are reported to have a low abundance of SCFA-producing bacteria, decreased levels of circulating SCFAs, and increased levels of fecal SCFAs compared to normotensive individuals (9, 38). In the HELIUS cohort study, BP was negatively associated with fecal SCFA-producing bacteria but positively associated with fecal SCFA levels (14). However, fecal SCFA levels do not necessarily reflect SCFA levels in the intestine but rather reflect SCFAs that were not absorbed by the host (39).

4-2. TMAO

The gut-microbiota-derived metabolite TMAO has a detrimental impact on cardiovascular health (40-42). TMAO is derived from the ingestion of food high in phosphatidylcholine, choline, and carnitine. TMAO has a proatherogenic and prothrombotic effect (43-45), and its circulating levels are associated with cardiovascular events and mortality (46). TMAO is also associated with hypertension. A meta-analysis conducted on a large population showed that individuals with high TMAO levels were more likely to develop hypertension than those with low TMAO concentrations (47). As a potential mechanism of TMAO-mediated aggravation of hypertension, experimental studies reported that TMAO prolonged the hypertensive effect of Ang II and facilitated Ang-II-induced vasoconstriction (48, 49).

4-3 Uremic toxins

Uremic toxins are metabolites that are retained under conditions of kidney dysfunction and have harmful effects on the host (50). Because various uremic solutes are derived from protein fermentation by colonic microbiota, the gut microbial status affects the plasma levels of these uremic toxins (22, 51, 52). *p*-Cresyl sulfate and indoxyl sulfate are representative microbiota-derived uremic toxins that exert multimodal harmful effects, such as the induction of oxidative stress, fibrosis, and inflammatory responses (53). Colonic fermentation of dietary tyrosine and tryptophan generates *p*-cresol and indole, which are metabolized to *p*-cresyl sulfate and indoxyl sulfate, respectively. Although these uremic toxins do not directly induce hypertension, their vascular toxicities promote vascular calcification, atherosclerosis, and increased arterial stiffness (54, 55).

5. Effects of the microbiota on antihypertensive drug and steroid hormone metabolism

5-1 Microbiota metabolism of antihypertensive drugs

The microbiota impacts the expression of drug-metabolizing enzymes in the host (**Table 1**). For example, the expression of cytochrome P450 (CYP) isozymes, which are xenobiotic/drug-metabolizing enzymes, was lower in germ-free mice than in conventional mice (56). In contrast, the expression of purine metabolism enzymes, including xanthine dehydrogenase, was higher in germ-free mice (57). In addition, the gut microbiota exerts drug-metabolizing effects on certain antihypertensive drugs (5, 58). Therefore, the effects of the microbiota on drug-metabolizing enzymes in the host and the drug-metabolizing activities of the microbiota may influence the therapeutic efficacy of antihypertensive agents. For example, the gut microbiota contributes to the drug metabolism of amlodipine, a representative calcium-channel blocker. When amlodipine was incubated with a human fecal suspension, it was metabolized to yield a pyridine metabolite (59). In addition, when rats were treated with oral antibiotics such as ampicillin, which transiently depleted the gut microbiota, the plasma concentration of amlodipine was significantly increased (the area under the curve increased by 2.3-fold compared with control rats). This indicated the involvement of the gut microbiota in the metabolism of amlodipine and highlighted the possibility that a decrease in the microbiota by antibiotics may in turn increase the bioavailability of amlodipine. In addition, the probiotic bacterial species *Lactobacillus casei* appears to affect drug metabolism activity, probably that of CYP3A4, in the intestinal mucosa (60). When nifedipine, a calcium-channel antagonist metabolized by CYP3A4, was administered into the intestinal loop of rats pretreated with or without *L. casei*, the maximum plasma concentration of nifedipine was 40% higher in *L. casei*-treated rats than in their untreated counterparts. These results suggest that probiotic treatment may affect the metabolic activity of drugs in the intestinal mucosa. Furthermore, an interesting case report showed that intensive antibiotic therapy improved BP control in patients with refractory hypertension(61). However, the importance of these drug-drug interactions mediated via microbial metabolism has been underestimated.

Antihypertensive medications, similar to various other nonantibiotic drugs, may alter the composition of the gut microbiota (62). Microbiota alteration may enhance/diminish the therapeutic efficacy of antihypertensive agents (63). Treatment with losartan, an angiotensin II type 1 receptor blocker, improved gut dysbiosis in hypertensive rats, and FMT from losartan-treated rats reduced BP in untreated rats, indicating that the microbial changes induced by losartan partly contributed to its BP-lowering effects (63). Similarly, candesartan, an angiotensin II type 1 receptor blocker, increased *Lactobacillus* abundance in hypertensive rats (64). Therefore, the microbiota modulates the drug-metabolizing enzymes and intestinal transport of the drugs (5), and antihypertensive drugs modulate microbiota composition. Nonetheless, only a limited number of studies have directly investigated the effects of the gut microbiota on the pharmacokinetics of antihypertensive drugs.

5-2 Microbiota metabolism of steroid hormones

The gut microbiota also plays a role in metabolizing steroid hormones such as the glucocorticoids corticosterone and cortisol (6). Antibiotic treatment with neomycin or vancomycin reduced BP in corticosterone-induced hypertensive rats, indicating the role of the microbiota in steroid metabolism (65, 66). These antibiotics transiently destroy most intestinal bacteria, preventing steroidal metabolism and the reabsorption of these metabolites via enterohepatic recirculation (6). The relationship between microbiota composition and the metabolism of L-thyroxine, a thyroidal hormone used in the treatment of hypothyroidism, was also reported in a clinical study (67).

Moreover, drug metabolism by the microbiota is involved in the pathogenesis of licorice-induced pseudohyperaldosteronism (**Figure 2**). Glycyrrhetinic acid derived from glycyrrhizin, which is present in licorice, inhibits the enzyme 11β-hydroxysteroid dehydrogenase type 2 (HSD2) in the kidney, resulting in inappropriate stimulation of the mineralocorticoid receptor by cortisol, which causes aldosterone-like effects (68). In this pathway, orally administered glycyrrhizin is poorly absorbed in the intestine (69). Glycyrrhizin is metabolized in the intestine into glycyrrhetinic acid via gut microbial β-glucuronidase-mediated bioconversion and then is absorbed into the intestine (70). Subsequently, glycyrrhetinic acid is further converted into active derivatives such as 18β-glycyrrhetyl-3-O-sulfate, which inhibits renal 11β-HSD2 and causes licorice-induced pseudohyperaldosteronism (71). Therefore, without the gut microbiota, glycyrrhizin intake probably could not cause licorice-induced pseudohyperaldosteronism.

6. Salt sensitivity and the microbiota

Gut microbiota composition can be influenced by external factors such as diet (7). Notably, high salt intake modulates gut microbial composition in rodents and humans (11). High salt intake is one of the major dietary determinants of increased BP (72). Recent data showed that high salt intake induced dysbiosis and affected salt sensitivity in hypertension. A landmark study showed that sodium intake rapidly depleted the prevalence of *Lactobacillus* sp. and *Lactobacillus*-produced intestinal indole-3-lactic acid, consequently inducing proinflammatory T helper 17 (Th17) cells (73). The induction of interleukin-17A produced by Th17 cells promotes renal sodium reabsorption through the upregulation of renal sodium transporters, including sodium hydrogen exchanger 3 expression and sodium chloride cotransporter activity, thus contributing to salt-sensitive hypertension (74). In addition, in this study, probiotic treatment of mice with *Lactobacillus murinus* prevented salt-sensitive hypertension. A high-salt challenge in humans also reduced the intestinal survival of *Lactobacillus* spp., increased Th17 cell numbers, and elevated BP. Furthermore, a high-salt diet reduced the levels of *Bacteroides fragilis* and arachidonic acid in the intestine, which increased intestine-derived corticosterone production and corticosterone levels in the serum and intestines, thereby promoting BP elevation (75). Corticosterone also promoted sodium absorption by activating mineralocorticoid receptors in intestinal epithelial cells (76). Moreover, a randomized controlled trial showed that dietary sodium reduction increased circulating SCFAs and decreased BP in adults with untreated hypertension (77). These data support a link between salt-sensitive hypertension and the modulation of the microbiota.

7. Oral microbiota and BP

In addition to the gut microbiota, the oral microbiota plays an intrinsic role in BP regulation. Oral bacteria convert dietary nitrate into nitrite, a precursor of nitric oxide, which lowers BP via its vasodilatory effects (78, 79). Some vegetables, such as raw spinach, beets, celery, and lettuce, contain high concentrations of nitrates (78). Nitrite generated by the oral microbiota may be responsible for producing circulating nitrates. A 7-day treatment with a chlorhexidine-based antiseptic mouthwash reduced oral nitrite production by 90% and plasma nitrite levels by 25% and consequently increased systolic BP by 3.5 mmHg (80). A relationship between the oral microbiota and obstructive sleep apnea-associated hypertension has also been reported (81). In addition, periodontitis affects hypertension (82). The prevalence of periodontitis in patients with cardiovascular disease and hypertension was higher than that in those without hypertension. Furthermore, a higher abundance of periodontopathic bacteria was detected in hypertensive subjects than in nonhypertensive subjects (82). A causal relationship between periodontitis and BP was also observed in a clinical cohort study (83).

8. Antihypertensive treatment targeting the microbiota

New treatment options for hypertension include pharmacological and nonpharmacological interventions targeting the microbiota. Various interventions using prebiotics (e.g., dietary fiber), probiotics (e.g., *Lactobacillus* spp.), and postbiotics (e.g., SCFAs) show potential antihypertensive effects. Several studies have yielded positive results with regard to probiotic interventions against hypertension. In a meta-analysis of randomized controlled trials, probiotics reduced BP if used in sufficiently high doses and for a minimum of 8 weeks (84). The consumption of probiotics such as *Lactobacillus* spp. decreased systolic and diastolic BP by 3.6 and 2.4 mmHg, respectively, compared with those in the control groups. Another systematic review showed that probiotic supplementation had a beneficial effect on hypertensive patients by reducing BP, body weight, and blood glucose, especially in those with diabetes mellitus (85). Furthermore, dietary interventions, such as fasting, altered the gut microbiota, reduced BP, and decreased body weight in patients with metabolic syndrome (86).

9. Perspectives

The microbiota plays an important role in regulating BP and modulating hypertension. Strategies that consider relevant host-microbiota interactions may represent new therapeutic approaches for hypertension. However, the observed associations between the microbiota and hypertension vary greatly among study groups according to the ethnicity, age, and sex of subjects (14, 87, 88), and these differences should therefore be considered. To support better transparency and improve the reproducibility and translation of findings on gut microbiome studies in essential and experimental hypertension, the best practice advice on the sampling and storage of fecal/cecal samples, DNA extraction, sequencing methods (including metagenomics and 16S rRNA), and computational analyses was reported (89). In future studies, advanced analytical approaches and comprehensive big data analyses of the gut microbiota may provide opportunities to uncover novel mechanisms underlying hypertension and provide new strategies to improve BP management based on the individual state of the microbiota. Large-scale interventional studies targeting the microbiota are also warranted.

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Figure legends

Figure 1. The relationship between blood pressure and the gut microbiota.

Figure 2. The role of the microbiota in the pathogenesis of licorice-induced pseudohyperaldosteronism.

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Figure 1

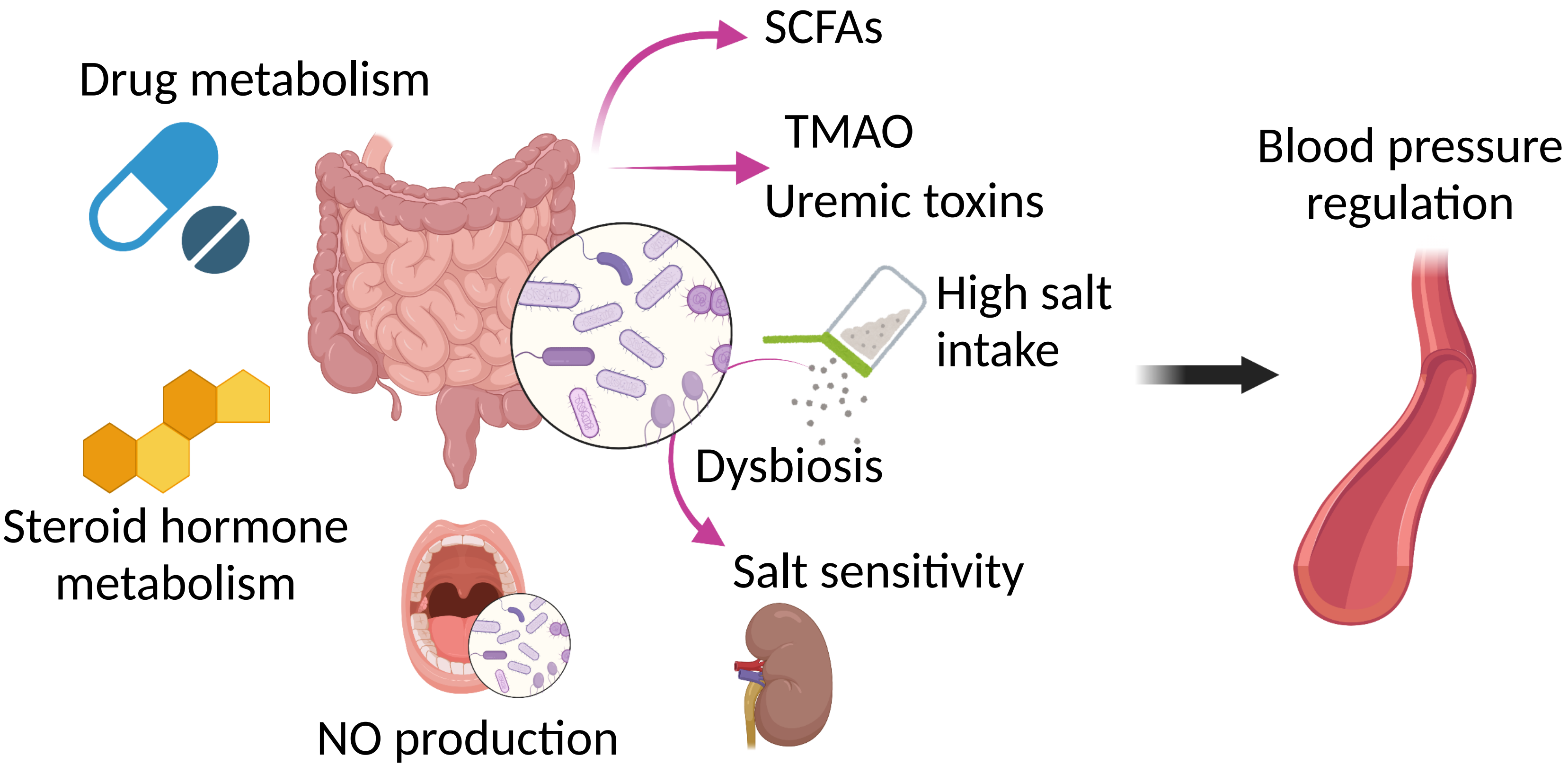
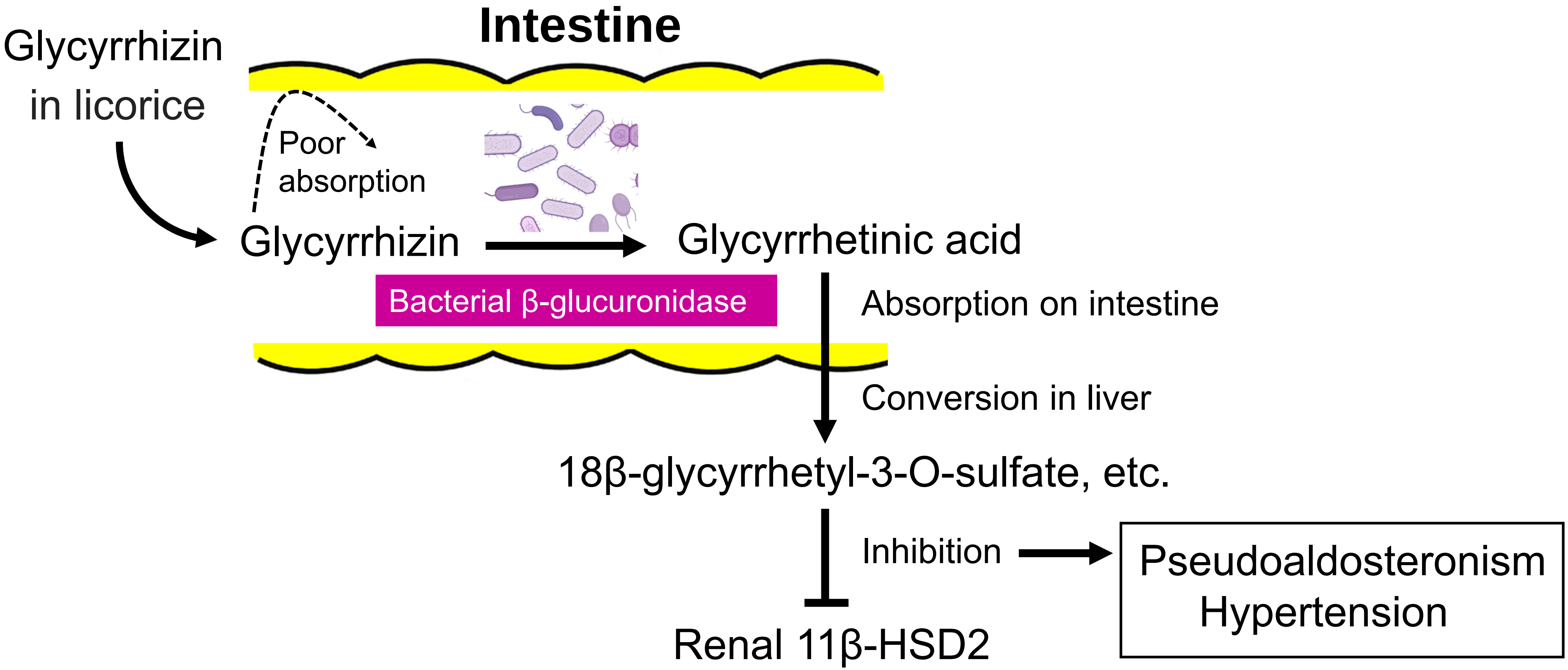

SCFAs
Drug metabolism
TMAO
Uremic toxins
Blood pressure regulation
High salt intake
Dysbiosis
Steroid hormone metabolism
Salt sensitivity
NO production

Figure 2


Intestine
Glycyrrhizin
in licorice
Poor
absorption
Glycyrrhizin
Glycyrrhetinic acid
Bacterial β-glucuronidase
Absorption on intestine
Conversion in liver
18β-glycyrrhetyl-3-O-sulfate, etc.
Inhibition
Pseudoaldosteronism
Hypertension
Renal 11β-HSD2