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Authors

Afsar, Baris
Vaziri, Nosratola D
Aslan, Gamze
et al.

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Review Article

Gut hormones and gut microbiota: implications for kidney function and hypertension

Baris Afsar, MD^a, Nosratola D. Vaziri, MD^b, Gamze Aslan, MD^c, Kayhan Tarim, MD^d, and Mehmet Kanbay, MD^{e,*}^a*Division of Nephrology, Department of Medicine, Konya Numune State Hospital, Konya, Turkey;*^b*Division of Nephrology and Hypertension, Department of Medicine, Schools of Medicine and Biological Science, University of California, Irvine, CA, USA;*^c*Department of Cardiology, Koc University School of Medicine, Istanbul, Turkey;*^d*Department of Medicine, Koc University School of Medicine, Istanbul, Turkey; and*^e*Division of Nephrology, Department of Medicine, Koc University School of Medicine, Istanbul, Turkey*

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Abstract

Increased blood pressure (BP) and chronic kidney disease are two leading risk factors for cardiovascular disease. Increased sodium intake is one of the most important risk factors for development of hypertension. Recent data have shown that gut influences kidney function and BP by variety of mechanisms. Various hormones and peptides secreted from gut such as gastrin, glucocorticoids, Glucagon-like peptide-1 impact on kidney function and BP especially influencing sodium absorption from gut. These findings stimulate scientist to find new therapeutic options such as tenapanor for treatment of hypertension by blocking sodium absorption from gut. The gastrointestinal tract is also occupied by a huge community of microbes (microbiome) that under normal condition has a symbiotic relationship with the host. Alterations in the structure and function of the gut microbiota have been shown to play a key role in the pathogenesis and complications of numerous diseases including hypertension. Based on these data, in this review, we provide a summary of the available data on the role of gut and gut microbiota in regulation of BP and kidney function. *J Am Soc Hypertens* 2016; ■(■):1–8. © 2016 American Society of Hypertension. All rights reserved.

Keywords: Intestinal hormones; kidney disease; microbiota; Na⁺/H⁺ exchanger-3.

Introduction

Hypertension is the leading cause of cardiovascular and renal diseases, including stroke, heart failure, coronary heart disease, and chronic kidney disease. Sodium plays a major role in the regulation of blood pressure (BP) and is one of the most critical factors in the pathogenesis of hypertension. There is a considerable body of evidence linking high salt intake with elevated BP and increased risk of cardiovascular disease.^{1–4} Salt sensitivity, defined as more than

5%–10% change in BP in response to a change in sodium intake, is associated with increased cardiovascular risk, even when the BP does not reach hypertensive levels.⁵

In recent years, studies have demonstrated a variety of ways with which gut-derived hormones such as gastrin and glucagon-like peptide-1 as well as byproducts of the gut microbial community participate in regulation of sodium homeostasis and arterial blood pressure. Gut microbiota can influence the production of various hormones such as serotonin, dopamine, and norepinephrine which can affect BP. In addition, microbial metabolites such as p-cresol sulfate, indoxyl sulfate, trimethylamine N-oxide (TMAO), and short chain fatty acids (SCFAs) can profoundly affect the cardiovascular system. The gut-derived hormones and byproducts of the gut microbiome have profound effects on the hosts' biology including the ability of the kidney to excrete sodium load and regulate BP.^{6,7} Recent studies have shown that inhibition of intestinal

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*Corresponding author: Mehmet Kanbay, MD, Koc University School of Medicine, Sariyer, Istanbul, Turkey. Tel: +902122508250; Fax: +902123454545.

E-mail addresses: mkanbay@ku.edu.tr, drkanbay@yahoo.com

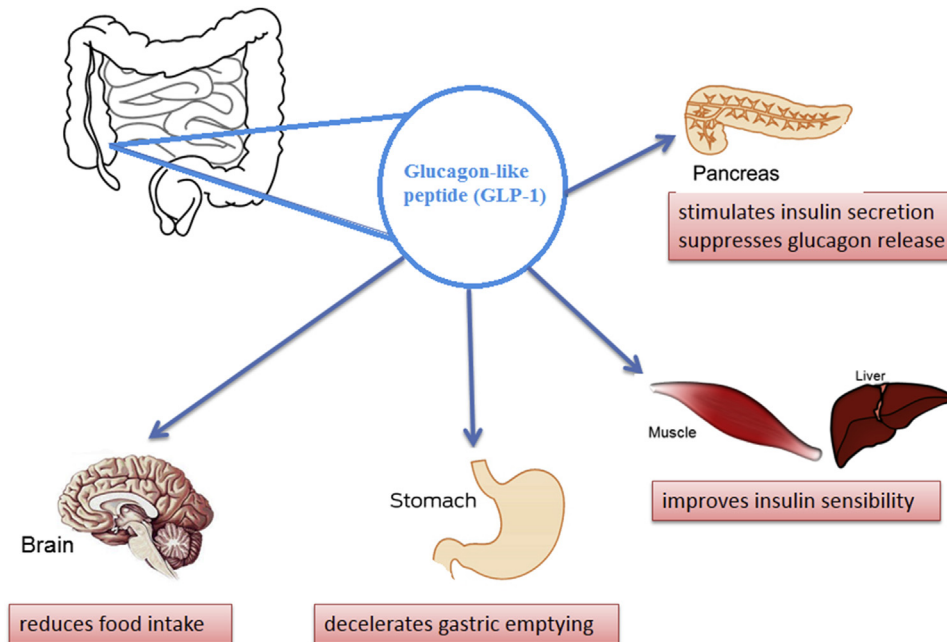


Figure 1. The renal effects of glucagon-like-peptid-1.

sodium absorption via blockade of the Na^+/H^+ exchanger 3 in rats can lower BP and protect against cardiovascular damage.⁸ This review provides a summary of the available data on the role of the gut-derived hormones and intestinal microbiota in regulation of sodium homeostasis and arterial pressure. In addition, novel drugs—targeting intestinal sodium transport and their efficacy in the treatment of hypertension are discussed.

Role of Gastrointestinal Tract in Regulation of Sodium Homeostasis and Arterial Pressure

As described below, gut may impact regulation of BP and urinary excretion of sodium by variety of mechanisms (Figures 1 and 2). Hormones and peptides secreted from gut have been shown to play a major role in regulation of sodium homeostasis and arterial BP. A number of biological conditions and therapeutic interventions can modify intestinal Na^+ absorption and hence arterial blood pressure by regulating the expression and activity of the intestinal sodium-proton exchanger subtype 3 (NHE3). A summary of the available data on the key factors involved in regulation of intestinal-renal sodium homeostasis and arterial BP are presented below.

Roles of Intestinal Hormones

Glucagon-like Peptide-1

Glp-1 is a 30 amino acid gut peptide generated through post-translational processing of the pro-glucagon gene product in the intestinal L-cells, predominantly localized

in the colon and ileum. Once released, this incretin hormone stimulates insulin secretion, suppresses glucagon release, decelerates gastric emptying, improves insulin sensibility, and reduces food intake.^{9,10} Glp-1 is rapidly degraded by the dipeptidyl peptidase-4 inhibitor (DPP-4), which circulates in the plasma and limits the half-life of Glp-1 to ~ 2 minutes.¹¹ Cumulative evidence supports a role for GLP-1 in modulation of renal function and regulation of BP.^{12–14}

The effect of chronic administration of GLP-1 was explored in a genetic model of experimental hypertension, the Dahl salt-sensitive rat, fed a high-salt diet for 2 week.

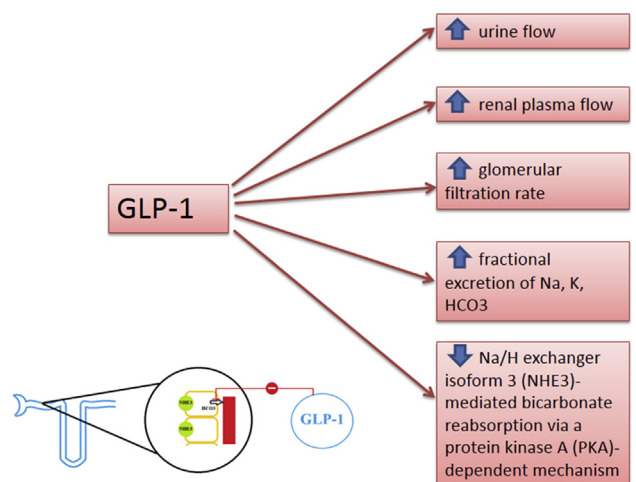


Figure 2. Gastrin effects on sodium metabolism.

Administration of GLP-1 attenuated significantly the development of hypertension, reduced cardiac and renal injury, and improved endothelial function in these animals. This was associated with increased urinary flow and sodium excretion, pointing to the natriuretic and diuretic properties and antihypertensive effect of GLP-1.¹⁵ Indeed, Schlatter et al. have detected the GLP-1 receptor in the primary porcine proximal tubular epithelial cells, where it inhibits sodium reabsorption.¹⁶

A recent study has shown that compared with the vehicle-treated rats, GLP-1-infused rats displayed increased urine flow, fractional excretions of sodium, potassium, and bicarbonate. GLP-1-induced diuresis and natriuresis were also accompanied by increases in renal plasma flow and glomerular filtration rate (Figure 1). In rat renal proximal tubule, GLP-1 significantly reduced Na/H exchanger isoform 3 (NHE3)-mediated bicarbonate reabsorption via a protein kinase A-dependent mechanism. Taken together, these data suggest that GLP-1 has diuretic and natriuretic effects that are mediated by changes in renal hemodynamics and downregulation of NHE3 activity in the renal proximal tubule.⁹

Liraglutide and DPP-4 inhibitors which enhance GLP-1 activity have been shown to lower blood pressure in animal models of obesity and hypertension and in humans with T2DM.^{17,18} In addition, glucocorticoids and aldosterone play a role in regulation of sodium absorption in the gastrointestinal tract. For instance, glucocorticoids regulate sodium uptake via induction of expression of a number of sodium/proton antiporters, particularly (sodium/hydrogen exchanger) member 3 (SLC9A3) in ileum and proximal colon.^{19,20} Likewise, via transcriptional upregulation and activation of SLC9A3 in the brush border membrane vesicles (BBMVs) of the proximal colon, aldosterone significantly increases sodium transport that is not observed when the BBMVs are derived from the ileum^{21,22} (Figure 3).

Gastrin

Gastrin is another enterokine which is involved in BP regulation. Sensing the amount of ingested sodium, by the stomach, is one mechanism by which sodium balance is regulated. Gastrin is secreted by G-cells in the stomach and duodenum and released into the circulation. Among the circulating gut hormones, gastrin is reabsorbed to the greatest extent by renal proximal tubules.²³ The oral intake of sodium, even in the absence of food, can stimulate gastrin secretion.²⁴ Sodium, in conjunction with D1-like receptors in G-cells of the stomach, increases the expression of gastrin.²⁵ Binding of gastrin to its receptor, cholecystokinin type B receptor (CCKBR), in human renal proximal tubular epithelial cells promotes natriuresis by inhibiting the Na⁺-H⁺ exchanger 3 and Na⁺-K⁺ -ATPase activities.²⁶ In fact, germline deletion of gastrin (*Gast*) or *Cckbr* gene in mice causes salt-sensitive hypertension.

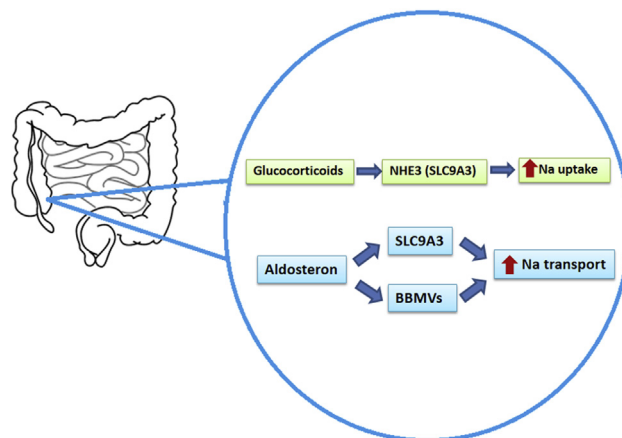


Figure 3. Glucocorticoids and aldosterone effect on sodium metabolism in the gut. BBMVs, Brush membrane vesicles; SLC9A3, Solute carrier family 9, subfamily A NHE3 (sodium/hydrogen exchanger 3).

Selective silencing of *Gast* in the stomach and duodenum of mice impairs their ability to excrete oral sodium load and increases their blood pressure. Thus, the gastro-renal axis, mediated by gastrin, can complement the effects of the pronatriuretic hormones, such as dopamine, by increasing sodium excretion after an oral sodium load. These studies in mice may be translatable to humans because the chromosomal loci of *CCKBR* and *GAST* are linked to human essential hypertension.²⁷

Gastrin has also been shown to decrease ileal absorption of sodium by increasing sodium secretion into the ileal lumen. The direct inhibitory effect of gastrin on sodium transport in the intestines may be complemented by gastrin-mediated stimulation of cholinergic or inhibition of sympathetic nerves.²⁸

Potential Role of the Intestinal Microbiome in Regulation of Sodium Balance and Arterial Pressure

The gastrointestinal tract is occupied by a huge community of microbes (microbiome) that under normal condition has a symbiotic relationship with the host. The enormity of the intestinal microbiome is evidenced by the fact that it accounts for over 65% of the weight of the fecal material.²⁹ Gut microbiota consists of a complex community of microorganisms that live in the digestive tracts of humans and animals and comprises the largest and most diverse reservoir of microorganisms.³⁰ The structure and function of the gut microbiota is determined by many factors including diet, physical activity, genetic, and epigenetic factors.⁶ The gut microbiota can regulate about 10% of the host's transcriptome, especially those genes related to immunity, cell proliferation, and metabolism.³¹

Alterations in the structure and function of the gut microbiota have been shown to play a key role in the pathogenesis and complications of numerous diseases including, obesity, type-2 diabetes, chronic kidney disease, inflammatory bowel diseases, dyslipidemia, cancer, allergic disorders, and hypertension among others.³² There are good and bad bacteria in the intestine. For example, Bacteroidetes are good, and Firmicutes are bad bacteria.³³ The Firmicutes and Bacteroidetes ratio was recently reported to be increased in spontaneously hypertensive rats, rats with angiotensin II-induced hypertension, and a small group of humans with essential hypertension. The oral administration of minocycline normalized the Firmicutes/Bacteroidetes ratio and BP in spontaneously hypertensive rats and rats with angiotensin II-induced hypertension.³⁴

Additional evidence comes from the Dahl salt-sensitive rats (SS) and Dahl salt-resistant (SR) rats. Although hypertension in the SS rats is exacerbated by a high-salt diet, BP is not altered by a high-salt diet in the SR rat.³⁵ It was recently hypothesized that genetic factors influencing the gut milieu may contribute to the development of hypertension in the SS rat.³⁵ If true, one such factor could be differences in the microbiotal composition/metabolites. In fact, recent study by Mell et al. revealed significant difference in cecal microbiotal compositions between the SS and SR rats.³⁶ Bacteria of the phylum Bacteroidetes were higher in the SS rats compared with the SR rats. Furthermore, the family S24-7 of the phylum Bacteroidetes and the family Veillonellaceae of the phylum Firmicutes were higher in the SS rats compared with the SR rats.³⁶

The influence of gut microbiota on the BP regulation is partially explained by the generation of short chain fatty

acids (SCFAs), including the beneficial SCFAs (acetate, butyrate, and propionate) and the nonbeneficial lactate by gut bacteria. SCFAs are produced by microbial fermentation of complex polysaccharides (starches and fiber) in the colon.⁷ These SCFAs can regulate BP by activating cell surface receptors including GPR43 (also known as free fatty acid receptor 2), GPR41, (also known as free fatty acid receptor 3), and olfactory receptor 78 (Olf78)^{6,37} (Figure 4). The increase in BP caused by SCFA-induced renin release from the afferent arteriole is mediated by Olf78 which can be counteracted by the vasodilatory action of GPR43.³⁸ In addition, via GPR43 activation, SCFAs suppress insulin signaling in adipocytes, thereby improving metabolism, in part, by inhibiting the accumulation of fat in adipose tissue.³⁹ By contrast, GPR41 increases energy expenditure by stimulating the sympathetic nervous system which could also raise BP.⁴⁰ In addition, both Olf78 and Gpr41 are expressed in smooth muscle cells of small resistance vessels.⁴¹ Propionate, a SCFA which has been shown to induce vasodilation *ex vivo*, produces an acute hypotensive response in wild-type mice. This effect is differentially modulated by disruption of Olf78 and Gpr41 expression.⁴¹

Toxic metabolites, such as p-cresol sulfate, indoxyl sulfate, and trimethylamine N-oxide (TMAO), are produced from fermentation of proteins by gut microbiota.⁴² Impaired urinary excretion in chronic kidney disease (CKD) results in accumulation in the body fluids of these toxic metabolites including TMAO which is derived from the metabolism of dietary choline, phosphatidylcholine (lecithin), and l-carnitine by microbiota by gut microbiota.⁴³ The role of these toxic metabolites in regulation of BP is not known and need to be determined.

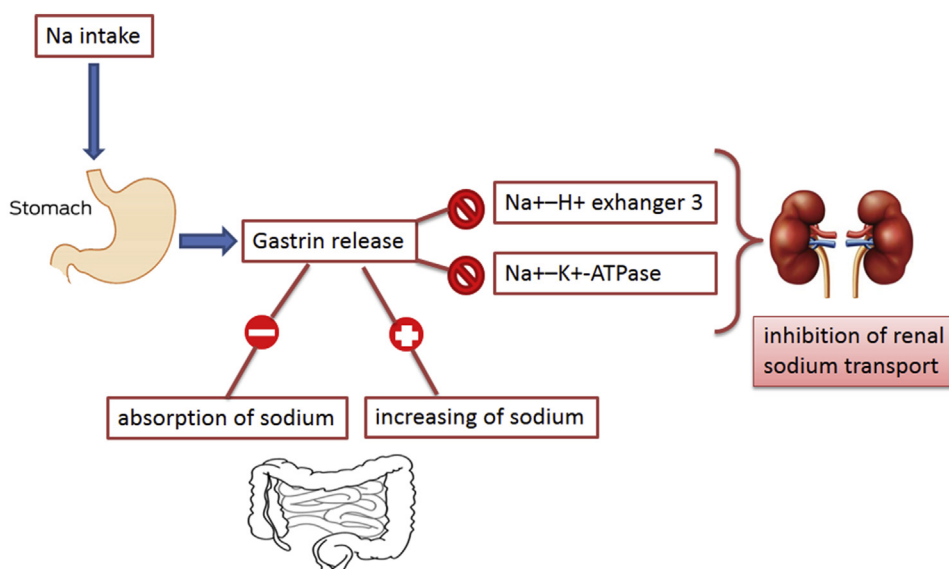


Figure 4. Gut microbiota on blood pressure (BP) regulation.

Sodium Absorption from the Intestine

There is a growing appreciation of the role of gastrointestinal tract in the regulation of blood pressure by sensing the amount of ingested sodium and the presence of a gut sodium sensor which has been a disputed topic.^{37,44} Indeed, high intake and intestinal absorption of sodium contribute to development of hypertension. The sodium-proton exchanger subtype 3 (NHE3) is an important mediator of sodium absorption in the gut. Limiting enteric sodium absorption is therefore an attractive option when renal sodium excretion is disturbed (because of impaired renal perfusion in heart failure, loss of functional nephrons in chronic kidney disease, or both as in cardiorenal syndrome).⁴⁵ Indeed, NHE3-knockout mice show lower BP compared with wild-type mice.⁴⁶ Thus, blockade of intestinal NHE3 to reduce intestinal sodium absorption could be a potentially novel strategy for treatment of hypertension⁴⁷ as is the case with commonly used diuretics which block renal tubular reabsorption of sodium. Animal studies have shown that by inhibiting intestinal NHE3-mediated sodium absorption, SAR218034 can serve as a new class of antihypertensive drugs.⁴⁷ In addition to the pharmacodynamic results in normal rats, the activity of SAR218034 has been assessed in two hypertensive rat models: lean hypertensive rats (loaded with 0.7% sodium chloride in drinking water) and obese hypertensive rats with hyperinsulinemia.⁴⁷ Sodium excretion and water content in stools increased and sodium excretion in urine decreased in these hypertensive rats, similar to the results observed with tenapanor administration in normal rats and rats with CKD. SBP was

significantly reduced in both rat models (Figure 5). Furthermore, when SAR218034 was given in combination with the ACE inhibitor ramipril, there was greater reduction of SBP compared with use of ramipril alone.⁴⁷ In addition, Tenapanor hydrochloride which is a novel NHE3 inhibitor has been studied in humans. This drug inhibits Na absorption in gut and increased fecal sodium content. In both normal rats and in healthy human volunteers, tenapanor dose dependently increased stool sodium content and reduced urinary sodium excretion. Tenapanor therapy moved between 20 and 50mEq of sodium into stool with twice daily dosing without affecting stool potassium or plasma electrolytes.^{8,48} However, after a nadir at 14 days, there is “escape” of enteric NHE3 blockade, possibly by upregulation of the epithelial sodium channel (ENaC) in the colon.⁸ The downside of this treatment is the rise in the osmotic fecal load which by necessity leads to watery feces or frank diarrhea. A solution would be to combine enteric blockade of NHE3 with intake of enough resin to bind the excess water.^{49,50} Unfortunately, complete analysis of fecal composition and changes in body weight was not reported in this study.

Regarding the systemic effects of these drugs, no notable trends were observed in urinary ammonium or chloride or serum bicarbonate levels following long-term administration of tenapanor to normal Sprague–Dawley indicating lack of significant impact on the acid–base homeostasis. Similar results were reported in healthy human volunteers, in whom tenapanor was well tolerated.⁸ However, supra therapeutic doses of tenapanor moderately reduced serum bicarbonate levels in nephrectomized rats. Therefore,

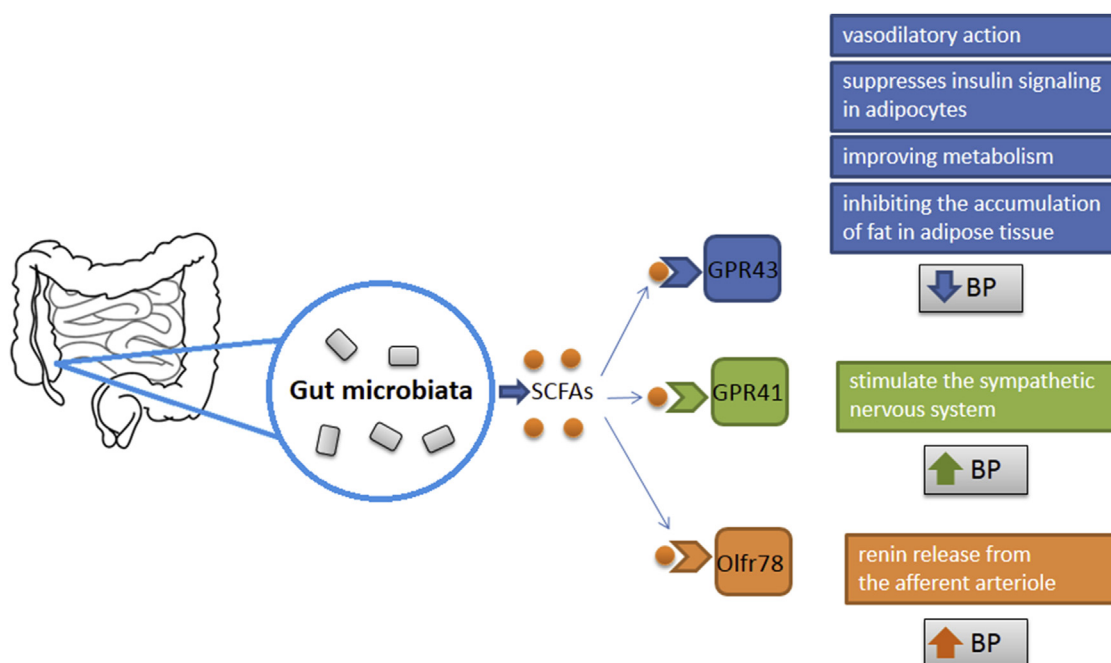


Figure 5. Tenapanor effects on accumulation of sodium in the gut.

acid–base status should be monitored in clinical studies of tenapanor since its chronic intestinal NHE3 inhibition can potentially alter acid–base balance in presence of renal disease.⁴⁸ It is of interest that in contrast to diuretics, NHE3 inhibitor treatment does not impair glucose metabolism and does not cause hypokalemia.⁴⁷

In rats with a high-salt diet-induced hypervolemia, cardiac hypertrophy and arteriosclerosis, administration of tenapanor-attenuated extracellular volume expansion, left ventricular hypertrophy, albuminuria, and hypertension in a dose-dependent fashion both prophylactically and after disease was established.⁸

NHE3 inhibition can also affect phosphorus levels. Oral administration of the NHE3 inhibitor, NTX3572, has been shown to increase stool phosphorus in Sprague–Dawley rats, and tenapanor administration has been shown to reduce urinary and serum phosphorus levels in a rat model of CKD and vascular calcification. In the same study, tenapanor reduced ectopic calcification, serum creatinine levels, and circulating fibroblast growth factor-23 concentration⁵¹ (Figure 6). Thus, these beneficial effects of the NHE3 inhibitors on phosphorus homeostasis and cardiovascular system should be more intensively studied. Indeed, randomized, placebo-controlled trials of tenapanor are underway in patients with diabetes who have CKD (ClinicalTrials.gov Identifier: NCT01847092) and in patients with CKD stage 5 on dialysis (ClinicalTrials.gov Identifier: NCT01764854).⁴⁸

As these drugs are novel, their side-effects are mostly unknown, and there are a number of potential concerns which need to be addressed. For example, diuretic treatment may affect NHE3 exchanger in the gut and result in further up-regulation of intestinal NHE3.²¹ This phenomenon may be particularly relevant in congestive heart failure and chronic kidney disease patients receiving high-diuretic doses.⁵²

Another issue is the activation of renin-angiotensin-aldosterone (RAS) system. Through the proposed mechanism of reducing intestinal sodium absorption, gut-restricted NHE3 inhibitors would be expected to increase RAAS activity (at sufficiently high doses) in a similar way to dietary sodium restriction and diuretic agent do.⁵³ Low-salt intake results in an activation of the RAS system, which serves to conserve sodium at the level of the renal tubule via increased reabsorption of filtered sodium and possibly explaining reduced renal sodium excretion in animals treated with SAR218034 (SAR), which is an unabsorbable specific NHE3 inhibitor. Thus, it is necessary determine whether treatment with SAR results in increased renin activity. If so, co-administration of ACE/angiotensin receptor blockers with NHE3 inhibitor treatment can be beneficial.⁴⁷

Future Perspectives

Based on aforementioned data, we believe that many issues need to be investigated and clarified. First, whether

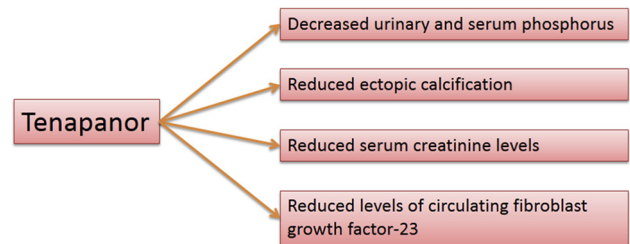


Figure 6. Tenapanor effects on phosphorus mechanisms.

hormones and peptides secreted by the gut such as Glp-1 and gastrin can be used for treatment of hypertension should be investigated. Second, apart from hormones and peptides, it needs to be determined whether they are involved in sodium absorption. Third, whether active manipulation to gut microbiota (eg, probiotic treatment) influences blood pressure. Fourth, whether correction of gut dysbiosis is correlated with hard outcomes such as cardiovascular and overall mortality needs to be investigated.

Conclusion

In conclusion, recent evidence suggests that alimentary tract is not only involved in digestive and absorptive physiology but also it is active endocrine organ. Additionally, gut microbiota is involved in various disease states such as hypertension obesity, cancer, and diabetes. Further research is necessary to highlight the importance of gut hormones and gut microbiota in terms of homeostasis.

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