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REVIEW

Novel Treatments from Inhibition of the Intestinal Sodium–Hydrogen Exchanger 3

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Abstract: Plasma membrane sodium–hydrogen exchangers (NHE) transport Na^+ into cells in exchange for H^+. While there are nine isoforms of NHE in humans, this review focuses on the NHE3 isoform, which is abundantly expressed in the gastrointestinal tract, where it plays a key role in acid–base balance and water homeostasis. NHE3 inhibition in the small intestine results in luminal sodium and water retention, leading to a general decrease in paracellular water flux and diffusional driving force, reduced intestinal sodium absorption, and increased stool sodium excretion. The resulting softer and more frequent stools are the rationale for the development of tenapanor as a novel, first-in-class NHE3 inhibitor to treat irritable bowel syndrome with constipation. NHE3 also has additional therapeutic implications in nephrology. Inhibition of intestinal NHE3 also lowers blood pressure by reducing intestinal sodium absorption. Perhaps, the most novel effect is its ability to decrease intestinal phosphate absorption by inhibiting the paracellular phosphate absorption pathway. Therefore, selective pharmacological inhibition of NHE3 could be a potential therapeutic strategy to treat not only heart failure and hypertension but also hyperphosphatemia. This review presents an overview of the molecular and physiological functions of NHE3 and discusses how these functions translate to potential clinical applications in nephrology.

Keywords: sodium–hydrogen exchanger 3, sodium–hydrogen exchanger 3 inhibitors, paracellular phosphate absorption pathway, hyperphosphatemia, chronic kidney disease, heart failure

Introduction: The Role of NHE3

Sodium–hydrogen antiporters or sodium–proton exchangers (NHE), of which there are nine total isoforms in humans, are a class of both plasma and organellar membrane proteins that transport Na^+ into the cell and H^+ out of the cell, as well as regulate luminal pH and cation composition of the intracellular compartments.[1] Isoforms of NHE have different tissue and subcellular distributions: some NHEs function primarily on the plasma membrane, and others are present on intracellular organelles.[1] NHE1 is expressed in the plasma membrane of virtually all tissues[2] and plays an important role in cardiac health.[3] NHE2 is expressed in the gastrointestinal (GI) tract and contributes to the maintenance of stomach pH and homeostasis, whereas NHE3 predominates in the GI tract and kidneys.[4,5] NHE4 and NHE5 are abundant in the stomach and brain, respectively.[6,7] NHE6-9 are expressed in the intracellular compartments of many organ system membranes, but of these NHE8 is the exception and expressed apically.[1,8–10]

NHE3 differs from other isoforms as it continuously recycles between the apical membrane of the epithelial and endosomal compartment, playing a key role in

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water and sodium homeostasis.[11] The physiological roles of NHE3 make it an attractive target for developing pharmacological inhibitors, which may be effective novel treatments for hypertension, constipation, diabetes mellitus, electrolyte disturbances (hyperphosphatemia), and congestive heart failure.

This review aims to present the molecular and physiological functions of NHE3 and how this information translates to clinical practice. The discussion will focus on the significance of NHE3 as a target for disease modification and recent advancements in the understanding of hyperphosphatemia and phosphate management in chronic kidney disease (CKD) patients.

Structure of the NHE3 Protein

All human NHE isoforms have similar structures, consisting of two functionally distinct domains.[12] However, the amino acid make-up of both domains varies among the NHE isoforms. An N-terminal of NHE3 is made up of 454 amino acids.[13,14] It is a 12 pass transmembrane domain that mediates ion exchange and the cytosolic C-terminus of 376 amino acids, regulates the transport rate, and interacts with the cytoskeleton and other ancillary molecules.[13,14] Separate regions of the C-terminal have been described as the "switch domain" for their role in setting NHE3 activity.[15,16] The C-terminal domain of NHE3 also binds to multiple proteins involved in NHE3 regulation.[16] Studies suggest that these regulatory proteins may form organized complexes that interact with NHE3 and with each other, thus stimulating or inhibiting the NHE3 activity.[17,18]

Evolution of NHE3 Across Species

NHE originated as intracellular exchangers first seen in yeast, slime mold, and plant species.[19] Of the two NHE subgroups, plasma membrane and intracellular, *NHE3* genes belong to the plasma membrane subgroup.[19] Human *NHE3* genes have their origins in the worm *NHX2* gene, known to be the first evolved plasma membrane NHE.[19] Studies in the *C. elegans* have shown that the ortholog of mammalian NHE3, CeNHX2, is recycled on and off the apical membrane of the gut epithelial cells.[20] This suggests that the emergence of CeNHX2 was necessary to maintain the proton gradient required for nutrient absorption.[20]

Genetics and Gain/Loss of Functions

NHE3, which is encoded by the *SLC9A3* gene, plays a critical role in the absorption of sodium and fluids and regulates acid–base homeostasis.[21] Studies of NHE3 knockout mice showed that lack of NHE3 results in reduced intestinal structural integrity, causing the animals to develop alkaline diarrhea, hyponatremia, and metabolic acidosis.[21] A study of individuals with congenital sodium diarrhea found that nine participants from unrelated families had an absent or mutated NHE3 protein, as demonstrated by SLC9A3 mutations.[22] Congenital sodium diarrhea is characterized by watery diarrhea after birth, high fecal loss of sodium, and metabolic acidosis.[23] Thus, loss or marked reduction of NHE3 function in humans was observed to have similar effects as those observed in NHE3 knockout mice.[21,22] To our knowledge, there are no models for a gain of function.

Mechanisms of NHE3 Regulation

NHE3 regulation falls into two forms: acute and chronic.[24–27] Acute regulation is a rapid, reversible process that occurs within minutes or hours.[28,29] NHE3 contains multiple phosphorylation sites,[27,30] and activity is modulated by protein kinases, including protein kinase A (PKA)[27] and serum- and glucocorticoid-inducible kinase 1 (SGK1).[30] Trafficking is another method of acute regulation. NHE3 differs from other NHE isoforms in that it can travel between the plasma membrane and intracellular compartments, and trafficking is the temporary compartmentalization of transport activity.[11] NHE3 is also capable of dynamic interaction with numerous proteins, and its activity can be modulated by protein-to-protein association.[17,31] Chronic NHE3 regulation, accounted for by transcriptional regulation, is an ongoing process that often involves multiple overlapping pathways.[32,33] Glucocorticoids, aldosterone, metabolic acidosis, serotonin, and proinflammatory cytokines have been shown to modify NHE3 expression.[32,34–36] There may also be a metabolic role in NHE3 activity. One example is the stimulation of renal NHE3 by fructose, which increases sodium reabsorption in proximal tubules.[37] Fructose can also sensitize the proximal tubule to angiotensin II.[38] These data may partially explain the mechanism by which a fructose diet induces renal injury and hypertension.[37,38] Additionally, chronic metabolic acidosis has been shown to increase NHE3 protein abundance in an animal model.[39]

Physiological Properties of NHE3

In addition to the kidney, which plays a major role in maintaining water and sodium balances, the importance of the GI tract in the regulation of sodium balance is increasingly recognized.[40,41] Expressed in the intestinal tract, kidney, and gallbladder, NHE3 is key to intestinal sodium and water absorption.[4,5,42] Present most abundantly in the GI tract and the kidneys, NHE3 helps the kidneys in their primary function of maintaining water and sodium homeostasis in the body through regulation of sodium absorption.[5] Key physiological functions of the NHE3 pathway include absorption of sodium, HCO_3, $NH4^+$, and water, and modulating the absorption of other nutrients (eg, dipeptides and amino acids) through the H^+ gradient.[24,43–46] The contribution of NHE3 to maintaining sodium homeostasis and acid–base balance is supported by recent results from an NHE3 knockout mouse model.[21]

However, NHE3 may be more than a sodium transporter – some studies have suggested an ability to modify other genes. In humans, NHE3 expression is decreased in patients with inflammatory bowel disease.[47] NHE3 knockout mice overexpress genes that induce the proinflammatory cytokines that target NHE3 as part of a homeostatic response to impaired sodium absorption.[48] In animal models, NHE3 deficiency compromises immune response and may be linked to changes to genes related to stress and inflammation.[48,49] Microarray analysis of NHE3 knockout mice showed that genes involved in response to stress, inflammation, and chemotaxis were altered, in addition to genes of ion transporters and ion channels.[49] NHE3 knockout mice have also been shown to have a compromised innate immune response.[48] This ability is consistent with studies showing changes in the expression level of genes in various brain regions in NHE1 knockout mice.[50]

Physiology of NHE3 Inhibition

NHE3 inhibition results in luminal sodium and water retention, leading to a general decrease in paracellular water flux and diffusional driving force.[51] Reduced intestinal sodium absorption and increased stool sodium excretion lead to modest intracellular proton retention that is proposed to induce a pH-sensitive conformational change in claudin proteins, directly reducing paracellular permeability specific to phosphate through the tight junction.[51] These physiological effects have been shown to translate to softer and more frequent stools, decreased blood pressure, and reduced phosphate concentrations.[52]

The role of NHE3 in maintaining sodium and water homeostasis is confirmed by pharmacological data from NHE3 inhibitor trials. The importance of NHE3 for intestinal sodium absorption is supported by reduced intestinal sodium absorption and increased renal sodium reabsorption in animal studies of a systemic NHE3 inhibitor for the treatment of hypertension.[53] These effects were consistent with reductions in urinary sodium and increases in fecal sodium seen in both animal and human trials of another NHE3 inhibitor.[54] Studies of intestinal epithelial cellular models demonstrated that an NHE3 inhibitor blocks NHE3-mediated proton efflux, resulting in a rapid (<1 minute) reduction in intracellular pH and a correspondingly rapid increase in transepithelial electrical resistance, which inhibits proton secretion coupled to sodium absorption by NHE3.[51] There are, to the best of our knowledge, no disputes on the differing roles of NHE3 in intestinal sodium absorption in animals and humans.

In contrast to sodium, the impact of genetic deletion of NHE3 on phosphate absorption in mice have been variable. Pan and coworkers reported that NHE knockout in mice results in a large and significant decrease in urinary phosphate excretion,[55] which would be consistent with reduced intestinal absorption. In contrast, Xue and coworkers did not report changes in phosphate absorption or excretion in their NHE3 knockout mouse model,[21] but this does not necessarily have serious implications for the understanding of NHE3 in humans; results from animal models of NaPi2b did not correspond to those seen in human trials,[56,57] and it is possible that NHE3 inhibitors are interacting with other pathways not present in animals.

Disease Targets for NHE3 Inhibition

The importance of sodium and water homeostasis for the proper functioning of multiple biological systems[58] makes NHE3 a potential therapeutic target for numerous disease states important to nephrologists,[53,59,60] such as hypertension, heart failure, diabetes mellitus, constipation, and hyperphosphatemia (Table 1).

Hypertension: Excess sodium increases the risk of hypertension and accelerates the progression of renal and cardiovascular dysfunction.[61–63] Reduction of GI sodium absorption through NHE3 inhibition may be an effective method of combating hypertension and associated negative clinical outcomes.[53,60] The natriuretic effects of the proximal tubule SGLT2 inhibitor empagliflozin, which lowers blood pressure, may be determined by NHE3.[64] A study of the NHE3 inhibitor SAR218034 found that the investigational

Table 1 Disease Targets for Sodium–Hydrogen Exchanger 3 (NHE3)

Disease Target	Pathophysiology Relevant to NHE3	Potential Mechanism of Action for NHE3 Inhibitors
Hypertension	● Excess sodium increases the risk of hypertension and accelerates the progression of renal and cardiovascular dysfunction[61–63]	● NHE3 inhibitors reduce intestinal sodium absorption[53]
Heart failure and diabetes mellitus	● NHE3 is upregulated in the proximal tubule of rats with heart failure, and enhanced NHE3-mediated sodium reabsorption in the proximal tubule may contribute to extracellular volume expansion and edema[75] ● Atrial NHE1 expression was significantly increased in patients with heart failure[76] ● Increased NHE3 activity is associated with impaired insulin sensitivity[78]	● NHE1 and NHE3 inhibitors may decrease the risk of heart failure by inhibiting atrial NHE1 activity and renal NHE3 activity, respectively ● Targeted NHE3 inhibitors may improve insulin sensitivity ● These may provide optimal management for both disorders
Constipation	● Low sodium concentrations cause a lack of water in the colonic lumen[83] ● This leads to dry, hard stools that are difficult to pass[84]	● NHE3 inhibitors reduce sodium absorption and increase water secretion into the intestinal lumen[52] ● This appears to result in softer stool consistency and increased intestinal transit time[52]
Hyperphosphatemia	● NHE3 plays a role in regulating paracellular intestinal phosphate absorption[51]	● NHE3 inhibitors create modest proton retention in cells, which is proposed to cause a conformational change in tight junction proteins. This conformational change reduces the permeability specific to phosphate through the paracellular pathway[51]

drug decreased sodium absorption in the gut and substantially reduced systolic blood pressure in rats.[60] Tenapanor, a novel targeted NHE3 inhibitor, has been shown to reduce blood pressure, fluid volume, and left ventricular hypertrophy in salt-fed nephrectomized rats.[54] Although human studies have been conducted,[54] the impact on hypertension has not been published yet as of the time of this paper.

Diabetes: Diabetic patients may also benefit from NHE3 inhibitors. In vitro study of both human and mouse jejunums found that NHE3 knockdown suppressed glucose uptake via sodium-glucose co-transporter 1 (SGLT1), implying an essential role of NHE3 in small intestinal glucose absorption.[65] Therefore, a potential clinical application of NHE3 inhibition is the treatment of type 2 diabetes by reducing intestinal glucose uptake.[65] Given that type 2 diabetes is almost 2.5 times as likely to develop in patients with hypertension compared to those with normal blood pressure,[66] diabetic patients may also benefit from the ability of NHE3 inhibitors to combat high blood pressure.

Heart failure and diabetes mellitus: Heart failure and diabetes mellitus are common, intertwined comorbidities.[67,68] Diabetes is an independent risk factor for heart failure,[69] and insulin resistance is associated with risk of heart failure.[70] The insulin insensitivity and adipokine abnormalities that

characterize diabetes contribute to heart failure,[70,71] and neurohormonal systems activated in heart failure (eg, norepinephrine, angiotensin II) negatively impact insulin sensitivity and microvascular disease in diabetes.[72,73] It is thought that a mechanism connecting these physiological activities is increased activities of NHE3 and NHE1.[74] Inoue et al found that NHE3 is upregulated in the proximal tubule of rats with heart failure by transcriptional, translational, and posttranslational mechanisms.[75] The study also suggested that enhanced NHE3-mediated sodium reabsorption in the proximal tubule may contribute to extracellular volume expansion and edema (hallmarks of heart failure).[75] Compared with patients without heart failure, atrial NHE1 expression was significantly increased in patients with heart failure with preserved ejection fraction and atrial fibrillation.[76] Impaired insulin sensitivity (linked to the progression of diabetes)[77] is associated with increased NHE3 activity.[78] Therapies that disrupt both NHE1 and NHE3 had a substantially greater impact on heart failure in diabetes patients in comparison to other factors like myocardial infarction or stroke.[76,79,80] A potential logical explanation for this effect is that such therapies are particularly effective when both NHE isoforms are upregulated. Empagliflozin, an SGLT2 inhibitor, inhibits NHE in human cardiomyocytes.[76] In patients with type 2 diabetes and high cardiovascular risk, empagliflozin reduced heart failure

hospitalization and cardiovascular death, with a consistent benefit in patients with and without baseline heart failure.[81] Sodium glucose cotransporter 2 may functionally interact with NHE3 in the proximal tubule, suggesting that SGLT2 inhibition could be an effective treatment for blood glucose effect-dependent and independent nephroprotective actions and reduction and cardiovascular mortality.[82] Therefore, it is logical to further explore the potential for systemic NHE inhibitors to decrease the risk of heart failure and improve glucose tolerance.[74]

Constipation: The mechanisms that lead to constipation make this complication another target for treatment with NHE3 inhibitors. Lack of water in the colonic lumen as a result of low sodium concentrations leads to dry, hard stools that are difficult to pass.[83–85] NHE3 inhibitors reduce sodium absorption in the gut, leading to increased water secretion into the intestinal lumen.[52,86] This may accelerate intestinal transit time and result in softer stool consistency.[52] An NHE3 inhibitor has been shown to increase stool sodium excretion and soften stool consistency in human trials; the effects of irritable bowel syndrome with constipation (IBS-C), a common GI condition characterized by abdominal pain and prolonged GI transit, were alleviated in trial participants.[87,88] The NHE3 inhibitor was well-tolerated, and diarrhea of mild-to-moderate severity was the most common adverse event (13.3%).[88] This therapy was approved by the FDA in September of 2019.[89]

Hyperphosphatemia: Over 80% of the patients with CKD on dialysis require treatment for hyperphosphatemia,[90] a condition associated with negative clinical outcomes.[91] Kestenbaum et al found that serum phosphate concentrations >3.5 mg/dL were associated with a significantly increased risk of death in CKD patients, and mortality risk increased linearly with each subsequent 0.5 mg/dL increase in serum phosphate concentrations.[92] Phosphate retention also drives increases in FGF23,[93] which is independently associated with all-cause mortality and heart failure,[94] and increases in PTH,[93] which is predictive of cardiovascular mortality.[95] Tenapanor is a first-in-class, minimally absorbed, small-molecule NHE3 inhibitor with a unique mechanism of action that effectively reduces phosphate levels.[51] Inhibition of NHE3 by this therapy reduced proton secretion coupled with sodium absorption, resulting in reduced sodium absorption and modest proton retention in the cells.[51] This modest intracellular proton retention generated is proposed to modulate tight junction proteins (claudins) resulting in increased transepithelial electrical resistance (TEER) and reducing permeability specific to phosphate, thereby decreasing

phosphate absorption through the paracellular pathway.[51] Models of NHE3 knockout cells demonstrated that the effect of tenapanor on transepithelial electrical resistance and the paracellular pathway is due exclusively to on-target inhibition of NHE3 and is likely due to decreased intracellular pH.[51] Onset of increased TEER and reduced paracellular phosphate permeability is near-immediate.[51] (Figure 1) When administered orally to rats, tenapanor acted exclusively in the GI tract. The systemic availability of tenapanor was well below its in vitro potency of 5 nM when tested through plasma pharmacokinetic studies, as well as autoradiography and mass balance studies performed with (14) C-tenapanor.[54] The plasma tenapanor levels were below the limit of quantification in >99% of the patients on dialysis receiving tenapanor.[96] Thus, tenapanor likely does not inhibit NHE3 in the kidney. Tenapanor acts specifically on sodium and phosphate and does not affect the overall balance of other ions such as potassium, calcium, and magnesium.[54] The in vivo specificity of tenapanor is highlighted by its lack of impact on chloride, an anion that likely has similar paracellular permeability characteristic to phosphate.[51]

Tenapanor effectively reduced phosphate levels in multiple clinical trials.[97–100] At 12 weeks, tenapanor administration lowered serum phosphorus from baseline concentrations of 8.1 mg/dL to 5.5 mg/dL in the efficacy analysis set.[97] In a long-term Phase 3 study, tenapanor administration lowered serum phosphorus in subjects from baseline concentrations of 7.7 mg/dL to 5.1 mg/dL at 26 weeks in the efficacy analysis set.[98] A recent trial that compared the effectiveness of a combination of tenapanor and binder vs placebo and binder showed that tenapanor plus binder resulted in a 0.65 mg/dL larger mean serum phosphate reduction from baseline compared to placebo plus binder.[100] The study included 236 patients undergoing maintenance dialysis with hyperphosphatemia (defined in this trial as serum phosphorus 5.5–10 mg/dL inclusive) despite receiving phosphate binder therapy (sevelamer, nonsevelamer, sevelamer plus nonsevelamer, or multiple nonsevelamer binders).[100] Almost twice as many patients treated with tenapanor and binder achieved phosphate <5.5 mg/dL compared to patients treated with placebo and binder (37–50% vs 18–24%, p<0.05).[100] This dual-mechanism approach may be particularly relevant for patients with persistent hyperphosphatemia.[100] Adverse events were largely limited to softened stool and a modest increase in bowel movement frequency, consistent with tenapanor's mechanism of action that increases stool sodium and water content.[97]
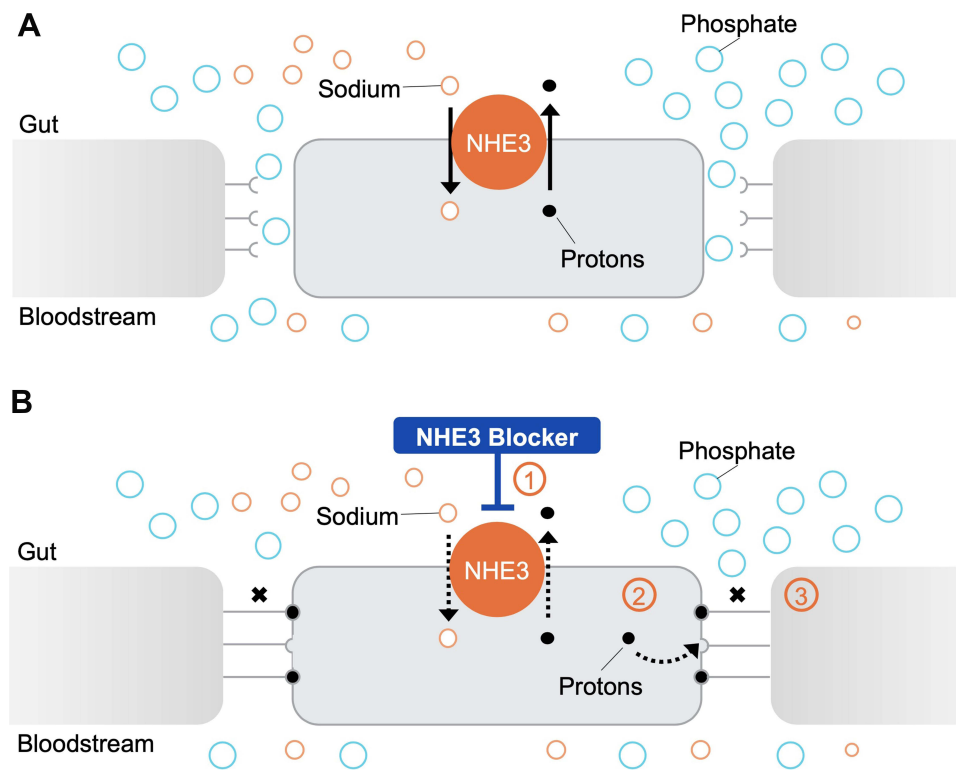
Figure 1 An NHE3 blocker reduces intestinal phosphate absorption through the paracellular pathway. (**A**) The intestinal paracellular phosphate absorption pathway: The sodium–hydrogen exchanger isoform 3 (NHE3) promotes the exchange of one sodium ion for one proton across the cell membrane.[5] The paracellular pathway, which is favored by electrical and chemical gradients, mediates the majority of intestinal phosphate absorption in humans.[51,109] Phosphate ions move down their electrical and chemical concentration gradients and are absorbed through the tight junction (TJ) complexes.[51,109] (**B**) Effect of an NHE3 blocker on the intestinal paracellular phosphate absorption pathway: Treatment with an NHE3 blocker inhibits sodium–proton exchange (1), leading to a modest intracellular proton accumulation.[51] This is proposed to cause conformational changes in tight junction proteins (2) and a consequent increase in transepithelial electrical resistance (TEER) that reduces paracellular permeability specific to phosphate (3)[51].

Phosphate homeostasis is intricately connected to the regulation of hormones and minerals affected in CKD mineral and bone disorder, such as vitamin D, calcium, fibroblast growth factor-23, and parathyroid hormone.[101,102] Thus, phosphate control via NHE3 inhibition may also have the potential to improve morbidity and mortality related to CKD-mineral and bone disorder.[103] Reduction of phosphate levels via NHE3 inhibition in the GI tract could also protect against vascular calcification,[104] a common complication of CKD associated with significant morbidity and mortality.[105,106] The effects of NHE3 inhibition and of phosphate lowering therapies in general on clinical outcomes will need to be examined in randomized controlled trials.

Summary and Future Directions

There is a gap between the latest biological understanding of the effects of NHE3 and clinical practice/therapy development.[51,54,107,108] Leveraging the latest understanding of the importance of NHE3 for multiple disease states may help researchers and clinicians achieve better patient outcomes. Inhibition of GI NHE3 results in increased sodium and water excretion as well as reduced paracellular permeability to phosphate. The effects of NHE3 inhibition translate to a range of systemic changes, including softer and more frequent stools, decreased blood pressure, and reduced phosphate concentrations. Reduced sodium absorption via NHE3 inhibition may be an effective treatment for hypertension, constipation, diabetes mellitus, and congestive heart failure. The clinical utility of NHE3 inhibition in these disease states will need to be tested in clinical trials. Targeted NHE3 inhibition has the potential to be particularly impactful for the treatment of hypertension, constipation, and achieving and maintaining normal phosphate homeostasis.

More broadly, the role of the GI tract in maintaining systemic homeostasis, alongside the kidney, should be considered in clinical practice and research as it is established that the GI tract is a site of absorption for solutes such as phosphate and sodium as well as water and acid–base balance. The connection between the GI tract and kidney and consideration of the GI tract as a site of focus to offload some of the kidneys' efforts certainly warrant further exploration.

Statement of Ethics

In this review article, no new research study was conducted that prospectively assigns human participants or groups of humans to one or more health-related interventions, and therefore, no patients were enrolled or subjected to therapies. Thus, there are no requirements for any ethical approval or informed consent. The process of developing this article complies with internationally accepted standards for research practice and reporting.

Acknowledgments

Funding

Disclosure

Dr Csaba P Kovesdy is a consultant for Abbott, Akebia, Amgen, Ardelyx, Astra-Zeneca, Bayer, Cara Therapeutics, Rockwell, Takeda, Tricida and Vifor. Dr Jeffery W Jacobs and Dr David Rosenbaum are employees of Ardelyx, Inc. In addition, Dr Jeffrey W Jacobs has a patent US8541448B2 issued to Ardelyx. The authors report no other conflicts of interest in this work.

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