



Pharmacologic inhibition of intestinal sodium uptake: a gut centric approach to sodium management

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Purpose of review

Impaired sodium excretion in patients with chronic kidney disease (CKD) can drive fluid overload and hypertension and accelerate CKD progression. Diuretics reduce fluid overload but require residual kidney function to work. Adherence to dietary sodium restriction is generally poor. Here, we review an alternative pharmacologic strategy aimed at reducing sodium absorption from the gut.

Recent findings

Genetic studies implicate the sodium/hydrogen exchanger isoform 3 (NHE3) as the major absorptive sodium transporter. Pharmacologic inhibition of apically expressed gut NHE3 offers the potential of reducing sodium absorption and fluid overload independent of kidney function and with better safety than systemic drugs. Two small-molecule inhibitors of NHE3 (tenapanor and SAR218034) with minimal systemic exposure reduce urinary sodium and increase stool sodium in a dose-dependent manner in rodents, with similar results observed with tenapanor in humans. These molecules also reduce blood pressure in rat models of CKD (tenapanor) and hypertension (SAR218034). Clinical trials of tenapanor in patients with CKD-related disorders are ongoing.

Summary

Pharmacologic inhibition of gut NHE3 may be a viable strategy for managing sodium load in patients with CKD or with sodium-sensitive hypertension in general. Ongoing clinical trials will shed further light on the potential benefits of this approach.

Keywords

chronic kidney disease, hypertension, non-systemic drug, sodium transport, sodium/hydrogen exchanger

INTRODUCTION

Renal injury, which may occur via a wide range of pathologic processes, leads to hyperfiltration by the remaining nephrons. This initially compensates for the loss of functional nephrons, but ultimately induces further glomerular injury and reduces the ability of the kidney to eliminate sufficient excess fluid and waste from the body [1]. Excess systemic sodium levels due to insufficient excretion by the kidney relative to dietary intake can cause hypertension and other clinical sequelae via an osmotically driven increase in the amount of fluid in the blood (fluid overload) [2,3].

Clinical and preclinical data shows that excess dietary sodium increases hypertension and accelerates renal and cardiovascular dysfunction in patients with chronic kidney disease (CKD) [3–7]. The converse observation has also been made in a recent Cochrane Database systematic review, which found that reducing salt intake lowered blood

pressure and proteinuria in patients with CKD [8]. Hypertension is itself a major promotor of decline in the glomerular filtration rate (GFR) [9,10] and a strong independent-risk factor for progression to CKD stage 5 [11,12]. Guidelines recommend restricting dietary sodium intake in patients with CKD [13,14]; however, results from various studies suggest that this approach is ineffective [15–18]. Indeed, dietary sodium restriction has recently been identified as a neglected therapeutic opportunity in patients with CKD [19].

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KEY POINTS

- Sodium accumulation in patients with CKD is an important driver of fluid overload and hypertension, which accelerate CKD progression.
- The sodium/hydrogen exchanger isoform 3 (NHE3) is apically expressed in the gut, wherein it has been shown by genetic studies to play the major role in sodium absorption.
- Selective, nonsystemic inhibition of gut NHE3 with tenapanor (rats and humans) and SAR218034 (rats) reduces urinary sodium and increases stool sodium, indicating reduced sodium absorption from the gastrointestinal tract.
- Tenapanor and SAR218034 also reduce blood pressure in rat models of CKD and hypertension, respectively.
- Pharmacologic inhibition of gut NHE3 may be a viable strategy for managing sodium and phosphorus in patients with CKD.

Current pharmacologic strategies for reducing fluid overload (e.g. diuretics) are primarily aimed at reducing osmotically driven fluid reabsorption by decreasing renal sodium reuptake. In this review, we discuss the clinical and biological rationale supporting an alternative, and potentially complementary [20], pharmacologic approach to reducing systemic sodium by reducing its absorption from the gut.

SODIUM, CHRONIC KIDNEY DISEASE AND BLOOD PRESSURE

Treatments for CKD mainly focus on managing comorbidities such as diabetes mellitus and hypertension, with the aim of reducing cardiovascular complications and slowing disease progression. Maintaining good blood pressure control is an important goal in order to slow CKD progression. This is typically achieved pharmacologically with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers, which reduce blood pressure by acting directly on the renin–angiotensin–aldosterone system (RAAS).

Studies in patients with CKD show that reducing or increasing sodium intake results in concomitant reductions or increases in blood pressure (i.e., these patients have sodium-sensitive hypertension) [19] and cardiovascular event risk, even in individuals who are already receiving RAAS blockers [7,21,22]. High sodium intake in patients with CKD also stimulates production of vascular endothelial growth factor-C (VEGF-C) [23]. VEGF-C is a key

factor in the recently discovered nonosmotic mechanisms of sodium storage in tissues that occur without commensurate water retention [24]. Another recent finding has been the sensitivity of endothelial cells to sodium levels. Increasing endothelial sodium content has been found to alter endothelial signaling to the vascular smooth muscle as well as to stiffen the vessel directly via osmotic swelling [25].

Studies in patients examining correlative relationships between age, hypertension and tissue sodium have revealed elevated tissue sodium levels in individuals with hypertension [26]. Inhibition of VEGF-C-mediated tissue sodium storage has been shown to induce sodium-dependent hypertension in rats [27,28]. Elevated VEGF-C in patients with CKD may, therefore, reflect an attempt to compensate for impaired sodium excretion and its effects on blood pressure by storing sodium in tissues. The demonstrated accumulation of sodium and its removal from tissues by haemodialysis further demonstrates the physiologic importance of this compartment in managing sodium and fluid balance in patients with CKD stage 5 [29**].

RAAS blockers render blood pressure sensitive to sodium [19]. Thus, patients with hypertension that is refractory to treatment with RAAS blockers (not just those with CKD) may benefit from reducing sodium uptake. In healthy individuals, SBP and DBP fall (or ‘dip’) at night; these individuals are classified as ‘dippers’. Those who do not exhibit this nocturnal fall in blood pressure are referred to as ‘nondippers’. In populations with CKD, nondippers are overrepresented and, because they are at elevated cardiovascular risk, may be of particular interest with regard to limiting sodium uptake [30,31]. Among patients with essential hypertension, nondippers may become dippers by restricting dietary sodium [32], and the time it takes for nocturnal blood pressure to fall correlates with daytime sodium retention [33]. These effects may be linked to circadian regulation of blood pressure via sodium handling [34–36], potentially involving direct regulation of sodium/hydrogen exchanger isoform 3 (NHE3; SLC9A3) [37] and other relevant sodium transporters [38–40].

MANAGING SODIUM AND FLUID: STUCK IN THE LOOP

As the GFR declines, less sodium is filtered leading to sodium retention and expanded extracellular fluid volume, whereas the failure of an appropriate and compensatory reduction of tubular reabsorption of sodium maintains fluid overload. Recent trials have highlighted the importance of fluid overload by confirming the efficacy of sodium restriction in

treating resistant hypertension without kidney disease [41] and the association between fluid overload and mortality risk in CKD [42]. The current standard of care for reducing sodium reabsorption in the kidney is delivered largely by thiazide diuretics (recommended for use in patients with CKD stages 1–3 [14]) and in some instances mineralocorticoid antagonists, in the latter case despite the risk of hyperkalaemia. Loop diuretics acting in the ascending loop of Henle are recommended over thiazides for use in patients with CKD stage 4 onwards, as they have been shown to be more effective in reducing fluid overload in patients with severely reduced GFR [14]. However, even potent loop diuretics only cause modest natriuresis, limiting their long-term therapeutic value as fluid overload is driven by extracellular sodium [43]. Furthermore, the efficacy of diuretics is to a significant extent dependent on renal function, which in the CKD setting is progressively declining. An alternative approach is to manage the sodium problem from the other side by preventing it from entering the system in the first place. This would naturally be expected to lead to reduced fluid overload and less demand on natriuresis, with a consequential reduction in hypertension and hypervolemia. One such method may be to reduce the absorption of sodium in the intestine using inhibitors of NHE3 that act locally in the gut.

MANAGING SODIUM VIA THE GUT: ROLE OF SODIUM/HYDROGEN EXCHANGER ISOFORM 3

In mammals, NHE3 is expressed primarily in the kidney and the gastrointestinal tract. In its native state, the orientation of the transporter in the apical membranes of renal and gastrointestinal tissues results in retention of sodium in the kidney and absorption of dietary and endogenous sodium from the lumen of the intestine. Although apical NHE transporters are known to compensate for one another and the intestine expresses three apical NHEs (NHE2, NHE3 and NHE8), genetic studies have implicated NHE3 as the major absorptive sodium transporter in both the intestine and the kidney [44]. As will be reviewed below, several phenotypes of NHE3 null mice can be mimicked preclinically by oral administration of small molecule inhibitors of intestinal NHE3, including reduced blood pressure and increased intestinal fluid.

It is important to consider species differences when interpreting potential compensatory mechanisms with respect to knockout models or pharmacologic inhibition. Although NHE3 is expressed at moderate-to-high levels in the human and rodent colon, we have observed between-species differences

in its expression along the small intestine (unpublished data), suggesting that it may contribute differently in different species [45,46]. How the effects of reduced NHE activity translate from animals into humans will depend on on-target potency (for drugs), as well as species variability in gut sodium and fluid flux, RAAS activation status and dietary sodium intake.

Based on the known biology of NHE3, gut-restricted pharmacologic inhibition of this transporter would be expected to reduce urinary sodium excretion (as would a reduction of dietary sodium intake) and increase the amount of sodium present in stool, which is typically very low. In addition, the pharmacodynamic effects of gut NHE3 inhibition would be expected to correlate with the concentration of drug dissolved in the gastrointestinal milieu as opposed to plasma drug concentrations, which should be negligible. 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 [16] with a concomitant increase in the concentration of sodium in the gut lumen. Discussion of comparative studies by Linz *et al.* [45] indicate that highly bioavailable inhibitors of NHE3 are significantly less active in the gastrointestinal tract than versions with minimal systemic exposure. Taken in sum and as reviewed below, data from multiple laboratories support a mechanism of action in which inhibitors of NHE3 act locally in the gut to reduce intestinal sodium uptake (Fig. 1).

RECENT PROGRESS WITH POTENTIAL THERAPEUTIC SODIUM/HYDROGEN EXCHANGER ISOFORM 3 INHIBITORS

The first report of a selective NHE3 inhibitor (although not designed to target gut-expressed NHE3 only) was in 1998 by Schwark *et al.* [36]. This molecule, designated S3226, was shown to be a potent (half-maximal inhibitory concentration [IC₅₀] 20 nmol/l) and selective inhibitor of NHE3 in a human kidney cell line [36]. Intravenous administration of S3226 was found to reduce fractional sodium excretion and exert protective effects on kidney function and structure in a rat model of acute renal failure, although we note Linz *et al.* [45] suggested that in their hands systemic NHE3 inhibitors had no significant effects on renal function [47].

More recently, we and other investigators have reported data on two small-molecule inhibitors of intestinal NHE3: tenapanor hydrochloride

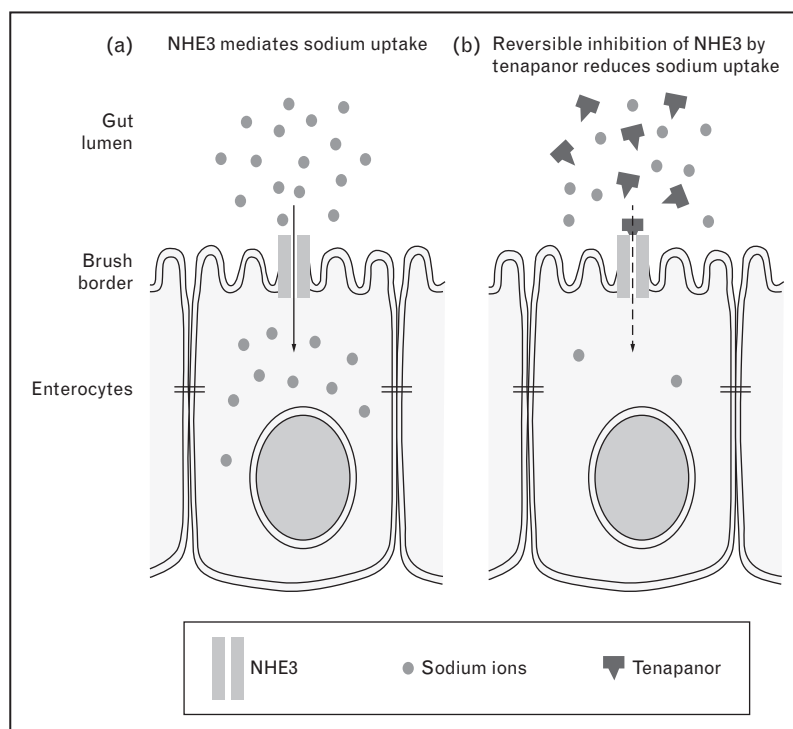


FIGURE 1. Proposed drug mechanism for reducing sodium absorption from the gut. (a) With normal sodium handling, the sodium/hydrogen exchanger isoform 3 (NHE3) plays a major role in facilitating absorption of sodium ions from the gut. (b) Reversible inhibition of apical NHE3 in the intestine by minimally systemic small molecules (such as tenapanor) reduces the sodium entering circulation, thus, theoretically reducing extracellular sodium and fluid overload.

(molecular weight 1218) and SAR218034 (molecular weight 512.4) [45,48^{***}]. In rats, both of these molecules exhibit minimal cellular permeability, low or unquantifiable concentrations in blood plasma, and, in the case of tenapanor, a major clearance pathway via stool as unmetabolized parent compound. To our knowledge, tenapanor is the only NHE3 inhibitor that has been evaluated in humans.

Several lines of evidence exist to support the claim that tenapanor and SAR218034 act locally in the gastrointestinal tract to reduce sodium absorption. First, tenapanor has been shown to reduce urinary sodium in a dose-dependent manner that correlates with luminal fluid mass and the concentration of the drug in the intestinal fluid [48^{***}]. Linz *et al.* [45] reported that the rate of sodium absorption was reduced in isolated intestinal loops in the presence of the gut-restricted NHE3 inhibitor SAR218034. Both inhibitors also appear to influence the RAAS pathway, thus, providing a likely mechanistic link between drug administration and reduced sodium uptake. Importantly, the gut-restricted NHE3 inhibitors also increase stool sodium, an observation consistent with reduction of sodium absorption from the gut.

In both normal rats and in healthy human volunteers, dose-dependent increases in stool sodium and reductions in urinary sodium have been observed following treatment with tenapanor (Fig. 2) [48^{***}]. These results were qualitatively similar to those seen with a sodium-deficient test meal in rats in the same study, and with a low-sodium diet in humans in another unrelated study [21]. Tenapanor moves between 20 and 50 mEq of sodium into stool with twice daily dosing without affecting stool potassium or plasma electrolytes [48^{***}]. In healthy volunteers, dose-dependent, moderate increases in Bristol stool form scores (1.5–2 units) are observed at doses in the therapeutic range [49].

No notable trends were observed in urinary ammonia or chloride following long-term administration of tenapanor to normal Sprague–Dawley rats, and serum bicarbonate levels were not altered, indicating that the acid–base chemistry was also not adversely affected. Similar results were reported in healthy human volunteers, in whom tenapanor was well tolerated [48^{***}]. However, supratherapeutic doses of tenapanor moderately reduced serum bicarbonate levels in nephrectomized rats in this study. Acid–base status should, thus, be monitored in clinical studies of tenapanor because its

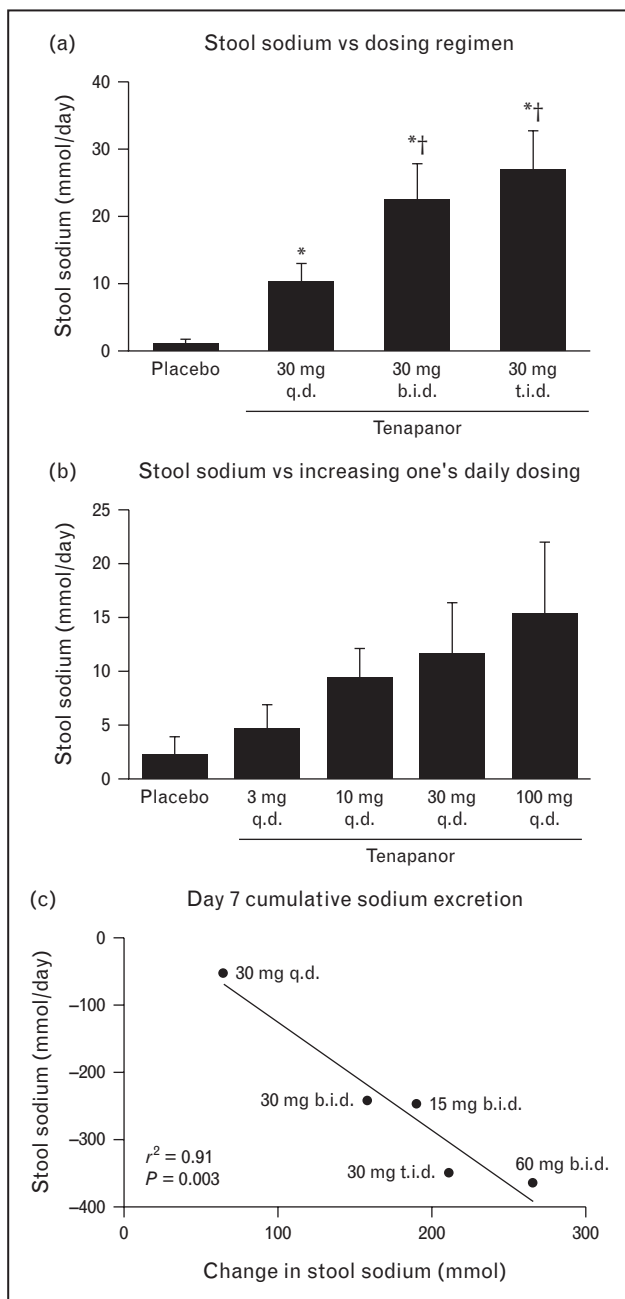


FIGURE 2. Effect of tenapanor on stool sodium and urinary sodium in healthy human volunteers. (a) Tenapanor 30 mg was given to healthy individuals once (q.d.) ($n = 6$), twice (b.i.d.) ($n = 10$), or three times (t.i.d.) ($n = 10$) daily for 7 days, and the average daily stool sodium was determined ($n = 10$ for placebo). (b) Once-daily doses of tenapanor of increasing strength (3, 10, 30 and 100 mg) were given to healthy human volunteers for 7 days ($n = 6$ per group, and $n = 10$ for placebo), and average daily stool sodium was determined. (c) Correlation between stool and urinary sodium content in response to tenapanor in healthy individuals. * $P < 0.05$ versus placebo, * $P < 0.05$ versus 30 mg once daily. Data are means \pm SEM. Data from [48[■]].

perturbation is a potential effect of intestinal NHE3 inhibition in renal disease.

In studies of five of six nephrectomized rats fed a high-salt diet and exhibiting hypervolemia, cardiac hypertrophy and arterial stiffening, tenapanor reduced extracellular volume, left ventricular hypertrophy, albuminuria and blood pressure in a dose-dependent fashion both prophylactically and after disease was established [48[■]]. In addition, rats with CKD given tenapanor and the ACE inhibitor enalapril showed reduced progression of cardiac diastolic dysfunction and improved arterial pulse wave velocity relative to rats given enalapril alone. Randomized, placebo-controlled trials of tenapanor are being conducted in patients with diabetes who have CKD (ClinicalTrials.gov Identifier: NCT01847092), and in patients with CKD stage 5 on dialysis (ClinicalTrials.gov Identifier: NCT01764854).

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 [45]. 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 in normal rats and rats with CKD. SBP was significantly reduced in both rat models. Furthermore, when SAR218034 was given in combination with the ACE inhibitor ramipril, there was an additive effect in terms of reducing SBP, compared with use of ramipril alone.

It should be noted that in addition to the effects of gut restricted NHE3 inhibition on sodium, phosphorus can also be affected. In Sprague–Dawley rats, oral administration of an NHE3 inhibitor (in this case, NTX3572) with low systemic exposure was found to increase stool phosphorus, and tenapanor decreased urinary and serum phosphorus in a rat model of CKD and vascular calcification [50[■]]. In the same study, tenapanor reduced ectopic calcification, serum creatinine levels, and levels of circulating fibroblast growth factor-23, which was recently shown to play a role in renal sodium handling and the control of blood pressure [51[■]]. Thus, tenapanor appears to have an effect on hyperphosphatemia through a mechanism that is currently unknown but clearly distinct from that of phosphate binders. A clinical study on the effects of tenapanor in patients with CKD stage 5 and hyperphosphatemia who are on haemodialysis was recently completed (ClinicalTrials.gov Identifier: NCT02081534).

A potentially intriguing aspect of the tenapanor story is the potential impact of genetic variation on NHE3 activity. Zhu *et al.* [52] recently published a

comprehensive analysis of NHE3 polymorphisms, of which three were found to be located in the C-terminal region, which is responsible for all known regulation of the NHE3 protein and predicted to disrupt basal NHE3 function and/or trafficking [53^{***}]. It is not known whether these polymorphisms are associated with any specific disease-related phenotypes. However, the authors postulate reductions in the response to drugs that may target NHE3 in individuals carrying these variants. Further, pharmacogenetic investigations may, thus, be warranted in ongoing clinical trials of tenapanor.

CONCLUSION

The key role of intestinal NHE3 in facilitating sodium and fluid absorption makes it an attractive target for pharmacologic intervention. Furthermore, the functional location of NHE3 on the apical surface of the gut allows pharmacologic inhibition by molecules with minimal systemic exposure, offering the potential benefits of greater safety and reduced risk of drug–drug interactions compared with systemic drugs. Importantly, the mode of action of an NHE3 inhibitor (unlike diuretics) does not require residual kidney function.

The effects of NHE3 inhibition by tenapanor and SAR218034 in normal, CKD and hypertensive rat models are consistent with the current understanding of the role of systemic sodium in the pathogenicity of renal disease, the known biology of the NHE3 transporter and the phenotype of NHE3-deficient mice. So far the pharmacologic activity of tenapanor appears to translate well from animal models to humans. Full results of ongoing clinical trials in patients with renal disease will shed additional light on potential benefits of this approach to sodium management.

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Conflicts of interest

A.G.S. is an employee and shareholder of Ardelyx, Inc., Fremont, CA, USA. P.J.G. is an employee and shareholder of AstraZeneca R&D, Mölndal, Sweden. Ardelyx, Inc and AstraZeneca are codevelopers of tenapanor.

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