The importance of intake: a gut feeling

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Abstract: Limiting enteric sodium absorption is an attractive option when renal sodium excretion is disturbed. An effective approach in the gut appears to be inhibition of the electroneutral Na^+/H^+ exchangers (NHE), in particular NHE3. Recently, fluid retention, blood pressure and target organ injury were limited in rats with cardiorenal syndrome when treated with the NHE3 inhibitor tenapanor. The downside was that the osmotic fecal load leads to watery feces. Tenapanor also induced marked reductions in enteric phosphorus absorption in rats with cardiorenal syndrome on a high phosphorus intake and resulted in marked reductions in renal injury and practically prevented vascular calcification. We have yet to discover the clinical relevance in volume terms and vascular calcifications in patients in relation to the tolerated dose. However, even if the tenapanor-induced reduction in sodium adsorption is limited in humins, combination of tenapanor therapy with diuretics may be an interesting option in selected patients.

Keywords: Cardiorenal; chronic kidney disease (CKD); dietary salt; Na^+/H^+ exchanger 3 (NHE3); tenapanor

Under normal circumstances, the stool contains negligible amounts of sodium, indicating that virtually all sodium that is ingested and that is secreted by the gut itself is being reabsorbed. Why is enteric sodium absorption not regulated? Perhaps, because of the osmotic effect of sodium chloride: the gut cannot generate free water and enteric excretion of excess sodium chloride would cause uncontrolled loss of water in the feces as occurs with diarrhea. As a consequence, mammals must excrete excess sodium reabsorbed in the gut via the kidney. Loss of renal function, or disturbed renal perfusion, therefore causes sodium retention, and hence, when non-osmotic stores are full, osmotic fluid retention and finally increased blood pressure and target organ damage.

Limiting enteric sodium absorption is therefore an attractive option when renal sodium excretion is disturbed (because of disturbed renal perfusion in heart failure, loss of functional nephrons in kidney disease, or both as in cardiorenal disease) (1). An effective approach in the gut appears to be inhibition of the electroneutral Na^+/H^+ exchangers (NHEs), particular NHE3 (2). In a milestone study fluid retention, blood pressure and target organ injury were limited in subtotally nephrectomized (NPX) rats with cardiorenal syndrome when treated with the NHE3 inhibitor

tenapanor. This novel drug worked both in a preventive study design (from the onset of renal ablation) and in a rescue study: 14 days after renal ablation when all disease characteristics (fluid retention, hypertension, albuminuria and left ventricular hypertrophy) were present. Importantly, tenapanor, while increasing fecal sodium content in rats, was practically not absorbed and therefore did not disturb NHE3 systemically. Tenapanor also inhibited sodium absorption and increased fecal sodium content in humans. However, the study does not provide information on the magnitude of volume depletion (acute weight change) or activation of the renin-angiotensin-aldosterone system that can be induced by tenapanor (which appears to be less effective in humans than in rats) as compared to volume depletion by the use of diuretics and/or dietary sodium restriction. Nevertheless, prospective randomized, placebo controlled trials are currently under way in patients with chronic kidney disease (CKD) and end-stage kidney disease (ESKD) (reference numbers NCT01764854 and NCT01847092).

The downside is that the osmotic fecal load will by necessity lead 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 (3,4), but
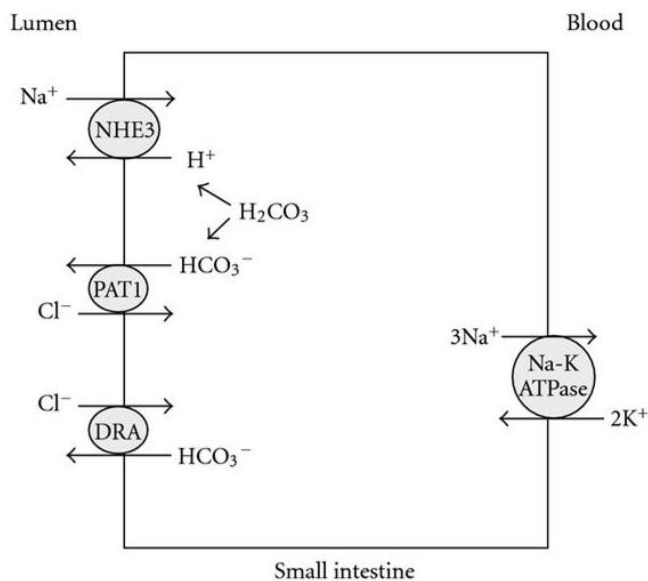
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Figure 1 Transporters in the small intestine (5). NHE3, sodium hydrogen exchanger 3: SLC9A3; PAT1, putative anion transporter 1: SLC26A6; DRA, down regulated in adenoma: SLC26A3.

this would make use of the new drug much less attractive. At present it is also not clear if long term use of tenapanor will affect nutrient absorption. Unfortunately, a complete analysis of fecal composition or even data on body weight change in the NPX rats was not provided in the study by Spencer *et al*. (2), but luminal fluid mass was doubled at the dose used. The argument that feces were not fully analyzed because the watery feces could not be fully separated from urine in the NPX rats is relevant for the dissection of direct and indirect effects of tenapanor on enteric and renal electrolyte excretion, but not relevant for macronutrient loss in the feces. Indeed, lower creatinine clearance in NPX rats treated with tenapanor vs. placebo, in the presence of less renal injury, suggests some loss of muscle mass, in addition to dampening of hyperfiltration due to volume contraction.

Judging by the changes in urinary sodium and chloride excretion, blocking enteric NHE3 appeared to induce parallel changes in enteric sodium and chloride absorption, suggesting that accumulation of sodium in the gut also increases chloride secretion via a chloride channel. Interestingly, after a nadir at 14 days, both urinary sodium and chloride excretion rates creep towards those of vehicle treated NPX rats, suggesting "escape" of enteric NHE3 blockade, possibly by upregulation of the epithelial sodium channel (ENaC) in the colon. Whether, in long term clinical studies, such "escape" will result in some loss of protective

effects of tenapanor remains to be seen. Furthermore, blocking enteric NHE3 results in less H^+ secretion, and indeed mild decreases in serum bicarbonate were observed, despite the amelioration of renal damage. In healthy rats there were transient increases in stool potassium, and the area under the curve for urine potassium and urine chloride appeared decreased, but data for these ions is lacking for the NPX rats. Exact mechanisms need to be teased apart but, based on known mechanisms of NHE3-dependent NaCl and H_2CO_3 exchange in the small intestine (*Figure 1*) (5), generally these effects were all expected. Clearly, in CKD and ESKD increases in stool potassium are welcome, but fecal loss of bicarbonate will need to be compensated. An interesting development in this context is the introduction of a novel selective cation exchanger that lowers serum potassium (6) while increasing serum bicarbonate (7).

Surprisingly a recent follow-up study by the same group showed that tenapanor induced marked reductions in enteric phosphorus absorption in NPX rats that were on high phosphorus intake in combination with calcitriol supplements (8). This is an accepted model of dystrophic calcification in the setting of CKD (9), and indeed in this model tenapanor also markedly reduced urinary phosphorus excretion as well as serum levels of phosphorus, calcium, creatinine and FGF23. Histology and urine analysis for albumin and KIM-1 revealed marked reductions in renal injury. Moreover, vascular and gastric calcification was practically prevented. About 70% of phosphorus uptake occurs in the small intestine. Of this >50% is due to passive transport secondary to sodium transport and water flux, and <50% is due to active transport mainly via the NaPi-IIb cotransporter (10). Nicotinic acid (niacin) is a drug that inhibits intestinal phosphate absorption by blocking the Na-Pi-2b sodium-dependent phosphate co-transporter (11). The mechanism is unclear, and may simply be the result of less passive phosphorus uptake secondary to the reduced water flux. It remains to be seen whether in other models of CKD-related dystrophic calcification or in humans with CKD similar protection is achieved. Whatever the mechanism, it appears to be entirely different from phosphate binders (8) or nicotinic acid. Furthermore, effect on renal function should not be judged merely by plasma creatinine or urea. Because of possible effects of NHE3 blockers on protein balance (see above), classic measurement of renal function with an exogenous compound, for instance inulin, are required. Nevertheless, these results are all very exciting, particularly in the light of the poor performance of current guidelines for oral phosphate binders in patients with CKD or ESKD (12).

However, NHE3 blockers will not have the beneficial effects of reduced intestinal uptake of colon-derived uremic toxins (13), as is the case with conventional phosphate binders that also bind uremic toxins (3).

We have yet to discover the clinical relevance in volume terms and vascular calcifications in patients in relation to the tolerated dose. However, even if the effect of tenapanor is limited in humans, combination therapy with diuretics may be an interesting option in selected patients. All in all, the introduction of tenapanor in treatment of patients with CKD and ESKD, heart failure and cardiorenal syndrome may herald a new era in their care. But, even if expectations are somewhat too high, findings in ongoing and projected studies that manipulate enteric sodium absorption will teach us a lot about the interaction between the gut and the kidney, and effects on non-osmotic sodium stores.

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