Role of intestinal Na^+/H^+ exchanger inhibition in the prevention of cardiovascular and kidney disease

Yan Jia[1], Guanghong Jia[2]

[1]Department of Biology, Cornell University, Ithaca, NY 14850, USA; [2]Division of Endocrinology, Diabetes and Metabolism, Department of Medicine, Diabetes Cardiovascular Center, University of Missouri, Columbia, MO 65212, USA

Correspondence to: Guanghong Jia, PhD. Assistant Professor, University of Missouri, D109 Diabetes Center HSC, One Hospital Drive, Columbia, MO 65212, USA. Email: jiag@health.missouri.edu.

Submitted Jan 05, 2015. Accepted for publication Feb 03, 2015.
doi: 10.3978/j.issn.2305-5839.2015.02.26
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.02.26

The expansion of extracellular fluid (ECF) volume increases the plasma volume, which consequently increases blood pressure and episodes of heart failure and chronic kidney disease (1). In the ECF, sodium chloride is the most abundant salt, and ECF volume increases linearly as the dietary intake of sodium increases (2). Furthermore, a normal sodium intake can also increase ECF volume in the end-stage renal disease patients (3). Thus, sodium balance is an important factor in the normal physiological functions of cardiovascular and renal system.

Excess dietary salt intake often causes disorders of sodium balance, which are common among older subjects because of age-related physiologic changes such as decreased thirst drive, impaired urinary concentrating ability, and reduced total body water (4) and therefore are independently associated with an increased mortality risk (5). First of all, excess dietary salt intake plays a key role in the development of hypertension through renal function impairment, vascular remolding, and activation of the sympathetic nervous system (6). The putative cellular pathway or sodium-sensing element linking plasma or central disorders of sodium to sympathoexcitation in salt-sensitive hypertension has been identified in the forebrain lamina terminalis and central sympathetic networks (6). These actions subsequently alter vascular resistance/capacitance, blood volume, cardiac output, arterial blood pressure, and kidney function resulting hypertension. Secondly, excess dietary salt intake is an important factor in contributing to heart failure and its prognosis. Decreased renal perfusion and neurohormonal activation in heart patients lead to enhanced proximal tubule inner medullary and collecting ducts reabsorption of sodium, water, and urea also result in the ECF volume expansion (7). One study has revealed that sodium levels within the reference range were associated with a differential prognosis in patients with heart failure. The commonly accepted reference range for serum sodium is 135-145 mmol/L and has low risk within normal thresholds. The upper half of the reference range (140-145 mmol/L) is associated with a low mortality risk (8). However, a serum sodium in the lower half (135-139 mmol/L) exhibits a twofold increase in the 5-year mortality risk in patients with heart failure regardless of the underlying cause and level of left ventricular compromise (8). Therefore, the maintaining the normal range of sodium concentration is very important in controlling the risk of morbidity and mortality in heart failure patients. Thirdly, excess dietary salt intake aggravates the progression of chronic kidney disease. An important reason that accounts for this is that patients with chronic kidney disease may be more susceptible to the development of dysnatremias by virtue of their diminished ability to maintain water homeostasis in the face of decreasing kidney function (9). Both lower and higher serum sodium has been found to represent both acute and chronic risk factors for mortality in the patients with chronic kidney disease (9).

The American Heart Association recommends people consume a maximum of 1,500 mg a day of sodium based on scientific evidence that it is the best approach for cardiovascular health while also providing an adequate intake of other important nutrients (10). However, the average American consumes about 3,400 mg of sodium a day, more than twice the recommended amount by the

American Heart Association (10). Thus, it is a good strategy to reduce sodium absorption in human gastrointestinal tract except for the reduction of sodium in the every diet. Several transporter families including the Na^+/H^+ exchanger (NHE) family mediate sodium absorption. The members of the NHE family are plasma membrane-bound antiporters that move extracellular Na^+ into cells in exchange for intracellular H^+. Five of the nine NHEs (NHE1–4, NHE8) are located in intestinal enterocytes, but only NHE2, NHE3, and NHE8 are expressed in the brush-border membrane of the intestinal epithelial cells (11). NHE2 is involved in gastric function. In comparison, NHE3 is an important player in Na^+ absorption and regulates physiological functions such as intracellular pH homeostasis, cell volume regulation, acid-base regulation, and electroneutral NaCl transport (11). NHE8 is another apically expressed NHE believed to have important roles in sodium absorption during early development (12). Therefore, inhibition of NHEs might be an important strategy in in modulating intestinal sodium and water absorption and preventing of cardiovascular and renal disease.

Recently, one study found that tenapanor, an inhibitor of the sodium-proton exchanger NHE3, plays a prominent role in handling sodium in the gastrointestinal tract and kidney (13). When administered orally to rats, tenapanor acted exclusively in the gastrointestinal tract to inhibit sodium uptake. In humans, tenapanor reduced urinary sodium excretion by 20 to 50 mmol/day and led to an increase of similar magnitude in stool sodium. In salt-fed nephrectomized rats, tenapanor reduced ECF volume, left ventricular hypertrophy, albuminuria, and blood pressure in a dose-dependent fashion. In additional, tenapanor prevented increases in glomerular area and renal injury. The present study provides evidences that sodium transport can be therapeutically altered in the gastrointestinal tract instead of the kidney and therefore identifies inhibition of NHE3 as a key therapeutic target in patients with cardiovascular and chronic renal disease. However, there are additional caveats to these studies that warrant considerations. First, sodium restriction may have adverse effects on the cardiovascular system and renal disease. Both hypo- and hypernatraemia indicate a markedly compromised prognosis in patients with heart failure and chronic kidney disease (8). Secondly, sodium restriction may alter various neural and humoral factors such as the activation of sympathetic nervous and renin-angiotensin-aldosterone systems, which induces and aggravate cardiovascular and chronic renal disease in a long term (14,15). Therefore, the impact of sodium intake should be discussed in a context of potential cardiovascular and renal risks and the recommended daily sodium intake. If NHEs inhibitions were to be used in patients, frequent electrolyte monitoring is necessary.

Overall, this study provides additional evidence that intestinal inhibition of sodium uptake with tenapanor results in modulation of ECF volume and cardiorenal protective effects. It is conceivable that therapeutic strategies targeting sodium balance disorders may lead to reduced morbidity and mortality in patients with cardiovascular and renal diseases. Obviously, further studies are warranted to elucidate and dissect the cellular and molecular mechanisms of inhibiting intestinal Na^+/H^+ antiport in the prevention of heart failure, kidney disease, and hypertension.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

References

1. McMahon EJ, Bauer JD, Hawley CM, et al. A randomized trial of dietary sodium restriction in CKD. J Am Soc Nephrol 2013;24:2096-103.
2. Labonté ED, Carreras CW, Leadbetter MR, et al. Gastrointestinal Inhibition of Sodium-Hydrogen Exchanger 3 Reduces Phosphorus Absorption and Protects against Vascular Calcification in CKD. J Am Soc Nephrol 2014;pii:ASN.2014030317.
3. Nanovic L. Electrolytes and fluid management in hemodialysis and peritoneal dialysis. Nutr Clin Pract 2005;20:192-201.
4. Shah MK, Workeneh B, Taffet GE. Hypernatremia in the geriatric population. Clin Interv Aging 2014;9:1987-92.
5. Liamis G, Rodenburg EM, Hofman A, et al. Electrolyte disorders in community subjects: prevalence and risk factors. Am J Med 2013;126:256-63.
6. Stocker SD, Monahan KD, Browning KN. Neurogenic and sympathoexcitatory actions of NaCl in hypertension. Curr Hypertens Rep 2013;15:538-46.
7. Shorr AF, Tabak YP, Johannes RS, et al. Burden of sodium abnormalities in patients hospitalized for heart failure. Congest Heart Fail 2011;17:1-7.
8. Deubner N, Berliner D, Frey A, et al. Dysnatraemia in heart failure. Eur J Heart Fail 2012;14:1147-54.
9. Kovesdy CP, Lott EH, Lu JL, et al. Hyponatremia, hypernatremia, and mortality in patients with chronic kidney disease with and without congestive heart failure.

Circulation 2012;125:677-84.
10. Coxson PG, Cook NR, Joffres M, et al. Mortality benefits from US population-wide reduction in sodium consumption: projections from 3 modeling approaches. Hypertension 2013;61:564-70.
11. Wang C, Xu H, Chen H, et al. Somatostatin stimulates intestinal NHE8 expression via p38 MAPK pathway. Am J Physiol Cell Physiol 2011;300:C375-82.
12. Abu-Ghefreh A, Khan I. A role of intestine in hypertension: mechanism of suppression of intestinal Na-H exchanger isoform-3 in spontaneously hypertensive rats. Clin Exp Hypertens 2013;35:543-9.
13. Spencer AG, Labonte ED, Rosenbaum DP, et al. Intestinal inhibition of the Na+/H+ exchanger 3 prevents cardiorenal damage in rats and inhibits Na+ uptake in humans. Sci Transl Med 2014;6:227ra36.
14. Jia G, Sowers JR. Endothelial dysfunction potentially interacts with impaired glucose metabolism to increase cardiovascular risk. Hypertension 2014;64:1192-3.
15. Jia G, Aroor AR, Sowers JR. Arterial Stiffness: A Nexus between Cardiac and Renal Disease. Cardiorenal Med 2014;4:60-71.

Cite this article as: Jia Y, Jia G. Role of intestinal Na^+/H^+ exchanger inhibition in the prevention of cardiovascular and kidney disease. Ann Transl Med 2015;3(7):91. doi: 10.3978/j.issn.2305-5839.2015.02.26

