Sodium Transporters in Kidney Role in Health and Disease

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Abstract
Sodium is an important cation and has an important role in BP regulation and ECF balance. Kidney plays an important role in sodium balance. Almost 99% of filtered sodium is reabsorbed. The absorption occurs via sodium transporters located in the various segments of the nephron. Each of these transporters has unique features and is blocked by a specific diuretic. The activating and inactivating mutations of these transporters are associated with important clinical syndromes. The understanding of these transporters and their mutations is essential for proper diagnosis and management of syndromes associated with the defects of these transporters. Also the knowledge of sodium transporters helps in understanding the role of kidney in pathogenesis of hypertension and pharmacodynamics of diuretic action. ©

INTRODUCTION
Sodium is the predominant extracellular cation and is of critical importance to the maintenance of extracellular fluid volume. The kidney is the dominant organ regulating the excretion of sodium. The kidneys typically absorb 99% of the filtered sodium load. A remarkable feature of the sodium reabsorptive process is the precision with which the final 1% of the filtered sodium load is regulated. The ability of kidneys to absorb large amounts of sodium with exquisite control relies on sequential actions of various segments of the nephron, each with highly specialized transport capabilities. The proximal tubule absorbs 60-70% of the filtered sodium, 15-25% is absorbed in the loop of Henle, 5-10% in the distal tubule and 1-2% in the collecting ducts (Fig. 1).

The collecting duct can produce urine that is almost sodium free (<10 meq/l). It is this sequential action of the different segments that permits high rates of sodium transport (proximal segments) and highly regulated sodium transport (distal segments).

Sodium Transporters in Health
The renal handling of sodium occurs through the following important transporters located through the nephron:
1) NHE (Sodium Hydrogen Exchanger) in the Proximal tubule
2) NKCC (Sodium Potassium Chloride Co-transporter) in the Loop of Henle
3) NCC (Sodium Chloride Co-transporter) in the Distal tubule
4) ENaC (Epithelial Sodium Channel)

The energy for the active transport processes is provided by the Na⁺K⁺ ATPase located in the baso-lateral membrane throughout the nephron.

1. NHE (Sodium Hydrogen Exchanger)
   NHE is the predominant isoform located in the apical membrane of the proximal convoluted tubule (Fig. 2) and transports Na⁺ into the cell in exchange of H⁺ which
in turn is secreted in the tubule lumen. The basolateral Na-K ATPase pump creates a favorable electrochemical gradient for Na entry into the cell which drives NHE. H⁺ secreted into the tubular lumen combines with HCO₃⁻ to form H₂O and CO₂, the latter diffuses into the cells. Carbonic anhydrase present in the tubular lumen allows rapid conversion of H₂CO₃ into H₂O and CO₂.

H⁺ secretion across the luminal membrane generates OH⁻ inside the cell which combines with CO₂ and forms HCO₃⁻ which leaves the cell via basolateral Na⁺-HCO₃⁻ co-transporter.¹ The Na transport in proximal tubule is linked to the transport of glucose, aminoacids and phosphate.

**NKCC (Sodium Potassium Chloride Co-Transporter):**

NKCC is located in the thick ascending limb of the Loop of Henle in the apical membrane and is the predominant mode of entry of sodium chloride in this segment (Fig. 3).

NKCC transports Na⁺, K⁺ and Cl⁻ into the cell in a stoichiometry of 1:1:2. Sodium and chloride are then transported to the peritubular fluid while K⁺ re-cycles back into the tubular lumen via the apical K⁺ channels. Blockade of the K⁺ re-cycling causes the luminal concentration of K⁺ to fall and limits net NaCl absorption. K⁺ current also provides for net K⁺ secretion by the TAL. For each Na⁺ ion transported into the cell by NKCC, 1 Na⁺ is absorbed via paracellular pathways. A small component of NaHCO₃ is absorbed through NHE which is also located in the loop of Henle, the absorption is presumed to be the same as in proximal tubule. The absorption of sodium chloride by NKCC is an example of secondary active transport.²³

**2. NCC (Sodium Chloride Cotransporter)**

It is the main sodium transporter of the distal tubule (Fig. 4) and absorbs 10% of the filtered Na⁺. Recent research has shown that the activity of NCC is regulated by WNK1 and WNK4 protein kinases. The sodium and chloride are transported in a ratio of 1:1.⁴

**3. ENaC (Epithelial Sodium Channel)**

The collecting duct is responsible for the final adjustment in urine concentration, K⁺ homeostasis, acid base balance and absorbs 2% of the filtered sodium load, the latter function is accomplished by the ENaC (Fig. 5). This channel is located in the apical membrane of the principal cells of the collecting duct and is highly sodium selective. Apart from the principal cells the collecting duct has intercalated cells which are mainly responsible for K⁺ resorption and play a role in H⁺ or HCO₃⁻ secretion.⁵

**4. Sodium Potassium ATPase (Na⁺K⁺ATPase):**

This is responsible for transport of sodium out of and potassium into the cells across the basolateral membrane. The pump is differentially expressed in the kidney with highest activity in the DCT followed by
loop of Henle and PCT in that order. Sodium transport is subject to regulation by physical factors and hormones.

**Sodium transporters in disease states**

Sodium transporters absorb major percentage of the filtered sodium and contribute to ECF and sodium homeostasis and blood pressure regulation. Sodium transporters maintain normal sodium balance and the mutations affecting these, form the basis of many disease states (Table 2).

**NHE Malfunction**

Malfunction of NHE is implicated in hypertension, hyperfiltration in diabetes mellitus, some forms of RTA and cyst formation in polycystic kidney disease. NHE also has a role in salt and water retention in nephrotic syndrome NHE is responsible for the acidification of lysosomes in PT and intralysosomal degradation of proteins. Malfunction of NHE results in intracellular protein accumulation and tubular damage. NHE is the main site of action of carbonic anhydrase inhibitor group of diuretics.

**NKCC Malfunction**

NKCC is the target for Loop diuretics. Mutations of the NKCC result in Bartter’s syndrome.

**NCC Malfunction**

NCC is the main site of action of Thiazide diuretics. It is subject to regulation by WNK kinases, a newly discovered group of protein kinases which are being explored as potential targets for new group of diuretics. Mutations of NCC result in Gitelman syndrome and Pseudohypoaldosteronism type II.

**Diseases of ENaC**

Mutations of ENaC lead to Liddle syndrome and Pseudohypoaldosteronism type I and are also implicated in the pathogenesis of essential hypertension.

**Role of sodium transporters in Hypertension**

Hypertension is the most common disease of the human population. Both genetic and non-genetic factors are involved and high salt intake has been proposed as the major risk factor. All forms of hypertension whether essential or secondary are due to a defect either of sodium transporters or their regulators.

**Monogenic hypertension** where a single gene defect has been identified. Some of the common monogenic hypertensive disorders are

- Liddle syndrome – ENaC channel gene
- Pseudohypoaldosteronism II – WNK kinase mutation which regulate NCC
- AME or Apparent Mineralocorticoid Excess Syndrome is another mendelian form of hypertension that is most often inherited as autosomal recessive disorder. Mutations in this disorder disrupt the 11β-OH steroid dehydrogenase gene which undirectionally metabolizes cortisol to cortisone and prevents cortisol from expressing

### Table 1: Sodium transporters

<table>
<thead>
<tr>
<th>Sodium transporters</th>
<th>Location</th>
<th>Clinical implications</th>
</tr>
</thead>
<tbody>
<tr>
<td>NHE</td>
<td>Proximal tubule</td>
<td>Role in hypertension, Sodium balance, Fluid homeostasis, diuretic action, RTA, PKD, Diabetic nephropathy, Nephrotic syndrome</td>
</tr>
<tr>
<td>NKCC 2</td>
<td>Thick ascending limb</td>
<td>BP regulation, Sodium and fluid homeostasis, Loop diuretics, Bartter’s syndrome</td>
</tr>
<tr>
<td>NCC</td>
<td>Distal tubule</td>
<td>BP regulation, Sodium and fluid homeostasis, Gitelman syndrome, Pseudohypoaldosteronism II, Action of thiazide diuretics</td>
</tr>
<tr>
<td>ENaC</td>
<td>Principal cells of Collecting duct</td>
<td>BP regulation, Sodium and Fluid Homeostasis, Liddle’s syndrome, Pseudohypoaldosteronism I, K+ sparing diuretics</td>
</tr>
</tbody>
</table>

### Table 2: Mutations of sodium transporters

<table>
<thead>
<tr>
<th>Channel defect</th>
<th>Type of defect</th>
<th>Clinical syndrome</th>
<th>Inheritance</th>
<th>Clinical features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>NKCC</td>
<td>Inactivating mutation</td>
<td>Bartter’s</td>
<td>AR</td>
<td>Polyuria, Metabolic alkalosis, Hypokalemia, PGE, Urine Ca</td>
<td>K+ supplements, Spironolactone, NSAIDs, ACEI, Indomethacin</td>
</tr>
<tr>
<td>NCC</td>
<td>Inactivating mutation</td>
<td>Gitelman’s</td>
<td>AR</td>
<td>Metabolic alkalosis, Hypokalemia, Hypocalciuria</td>
<td>K+ supplements, Spironolactone</td>
</tr>
<tr>
<td>NCC</td>
<td>Activating mutation</td>
<td>Pseudohypoaldosteronism II (Gordon’s)</td>
<td>AD</td>
<td>Hypertension, Hyperkalemia, Reverse of GS</td>
<td>Thiazides, Loop diuretics</td>
</tr>
<tr>
<td>ENaC</td>
<td>Activating mutation</td>
<td>Liddle’s syndrome</td>
<td></td>
<td>Monogenic HT, low renin, low aldosterone, volume expanded</td>
<td>Amlodipine, Salt restriction</td>
</tr>
<tr>
<td>ENaC</td>
<td>Inactivating mutation</td>
<td>Pseudohypoaldosteronism I</td>
<td>AD/AR</td>
<td>Salt wasting, Hypotension, High renin, High aldosterone, hyperkalemia</td>
<td>Salt supplementation</td>
</tr>
</tbody>
</table>
mineralocorticoid effects in the target tissues. As a result of this mutation a characteristic picture of mineralocorticoid excess is seen with hypertension, hypokalemia and metabolic alkalosis.

- Glucocorticoid Remediable Hypertension (GRE) is a rare autosomal dominant form of hypertension which is caused by a chimeric gene duplication arising from unequal crossing over such that the regulatory sequences of steroid 11 β-hydroxylase control the expression of the coding sequences of aldosterone synthetase. Increased aldosterone activates ENaC. The production of 18-hydroxy cortisol and aldosterone metabolites is increased and can be suppressed by dexamethasone through suppression of ACTH secretion. These three forms of hypertension can be distinguished by urinary steroid profiles.

**Essential hypertension (EH):** Na⁺ transporters also have an important role in the pathogenesis of EH.

Activating mutations of the ENaC are uncommon in EH but the patients of EH show polymorphism in the genes, which regulate the activity of ENaC channel.

- About 6% of patients of EH have T594M missense mutation of ENaC. This results in low renin hypertension and is more common in blacks as compared to the whites. Females are more commonly affected than males. Urine Aldosterone / K⁺ ratio is low.

- In African blacks, 35% with low renin Hypertension have G442V mutation of ENaC with similar clinical features as above.

- An adducin gene has been identified, polymorphisms and interaction of this gene with aldosterone synthetase gene favors sodium resorption leading to hypertension. Functional differences between DD and II polymorphism are magnified in presence of these gene variants.

- RBC NHE and Na⁺-Li⁺ co-transporters have also been implicated. Thus the basic defect in hypertension lies in the kidney and directly involves the sodium transporters or indirectly the regulators of these transporters.

**Sodium Transporters and Diuretics**

Diuretics bring about natriuresis and diuresis by acting on and blocking the activities of the various sodium transporters located in the different nephron segments (Table 3) (Fig. 6).

- **Carbonic anhydrase inhibitors** These act on the proximal tubule and inhibit carbonic anhydrase enzyme and inhibit the NHE and hence cause natriuresis. These are mild diuretics. These result in metabolic acidosis and hypokalemia.

- **Loop diuretics** are the most potent of all classes of diuretics and are hence known as the high ceiling diuretics. These are effective even at a GFR less than 15 ml/min. They reach the tubular lumen by secretion in the proximal tubule. The prime site of action of Loop diuretics is the thick ascending limb of the loop of Henle where they block the NKCC. LD increase acid excretion and cause metabolic alkalosis. Bartter syndrome shares homology with the actions of loop diuretics.

- **Thiazides**

  The major site of action of Thiazides is the early distal convoluted tubule (NCC) where they block 40% of coupled resorption of Na⁺ and Cl⁻. The action of thiazides resembles Gitelman syndrome.

- **K⁺ sparing diuretics**

  K⁺ sparing diuretics comprise two different classes of drugs

  1) Those which do not interact with aldosterone receptors (amiloride, triamterene)

  2) Competitive aldosterone antagonists (spironolactone)

  Distal K⁺ sparing agents act on the principal cells in the late distal convoluted tubule, initial connecting tubule and cortical collecting duct where they inhibit luminal sodium entry. These drugs cause a modest short term natriuresis.

<table>
<thead>
<tr>
<th>Site of action</th>
<th>Drug name</th>
<th>Mechanism</th>
</tr>
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<tbody>
<tr>
<td>PCT</td>
<td>Acetazolamide</td>
<td>NHE</td>
</tr>
<tr>
<td>Loop of Henle</td>
<td>Frusemide</td>
<td>NKCC</td>
</tr>
<tr>
<td>Early DCT</td>
<td>Thiazides</td>
<td>NCC</td>
</tr>
<tr>
<td>Late DCT</td>
<td>Amiloride</td>
<td>ENaC</td>
</tr>
<tr>
<td>Collecting duct</td>
<td>Spironolactone</td>
<td>Mineralocorticoid antagonist</td>
</tr>
</tbody>
</table>

Fig. 6: Diuretics and sites of action
Use of diuretics blocking sodium absorption in one segment of the nephron leads to hypertrophy of other nephron segments and consequent increased sodium absorption in these segments leading to diuretic tolerance. Combining different classes of diuretics acting on different segments of the nephron can minimize this.

Newer class of diuretic agents blocking WNK kinases are being developed.

What's new?

Studies demonstrate that the normal kidneys excrete readily detectable quantities of Na⁺ transporter proteins from the proximal tubule (NHE3), the thick ascending limb of Henle’s loop (NKCC2), and the distal convoluted tubule (NCC). They also confirm the presence of aquaporin-1 and aquaporin-2 in urine. Although we do not know the mechanisms involved in excretion of these Na⁺ transporter proteins, it seems likely that the presence of these proteins in urine will be exploitable in clinical studies in much the same way as have measurements of aquaporin-2 in urine. For example, profiling of Na⁺-1 transporters in urine could be useful in detecting and classifying acute renal failure, classifying inherited disorders of Na⁺ excretion, e.g., Bartter’s syndrome and Gitelman’s syndrome, or identifying renal defects associated with hypertension.16

REFERENCES