Diuretics

having the quality of exciting excessive excretion of urine. OED

Inhibitors of Sodium Reabsorption
Saluretics not Aquaretics
Sodium Absorption

Entry into the Cell
down an electrochemical gradient
Na channel, or Na coupled solute carriers

Exit into the blood by the Na:K ATPase

The Na$^+\,\,K^+$ ATPase

Located in the basolateral membrane of Renal Tubular Cells
Inhibited by the cardiac glycosides digoxin and ouabain

Nielsen et al., Amer. J. Physiol.277:F257. 1999
Pathway of Salt and Water Absorption in the Proximal Tubule

$\text{Net Flux} = \text{Trans-cellular} - \text{Leak}$
Carbonic Anhydrase Inhibitors

**Acetazoleamide**

“**Diamox**”

Oral absorption
Readily Filtered
Inhibits membrane bound and cytoplasmic carbonic anhydrase
inhibits H⁺ secretion; i.e. HCO₃⁻ Reabsorption
Increases delivery of NaCl and NaHCO₃ out of the PCT

Can cause Metabolic Acidosis

---

**H⁺ Secretion in the Proximal Tubule**

- Na⁺
- HCO₃⁻
- C.A.II
- CO₂ + OH
- H⁺ + HCO₃⁻
- CA IV
- CO₂ + H₂O
- NHE₃  Na:H Exchanger
- H⁺ translocating ATPase
- NBC  Na:HCO₃ cotransporter
**H⁺ Secretion in the Proximal Tubule**

after Carbonic anhydrase inhibition

\[
\begin{align*}
\text{H₂O} & \quad \text{H⁺} + \text{HCO}_3^- \\
\text{HCO}_3^- & \quad \text{CO}_2 + \text{OH} \\
\end{align*}
\]

**Osmotic Diuretics**

-Mannitol
- Urea
- Glucose

Given intravenously usually
Readily Filtered
Poorly reabsorbable in the nephron
Obligatory water retention in the lumen
Increase delivery of NaCl and water out of all segments
Rapid urine flow decreases NaCl and water absorption
Increases formation of dilute urine
Sodium Absorption in Thick Ascending Limb

**NKCC**  
Na:K:2Cl Co-transporter  
Furosemide sensitive cotransporter

**ROMK**  
K channel

**CLC-Kb**  
Chloride Channel

Apical Transporters of the Thick Ascending Limb

**NKCC**  

**ROMK**

Nielsen et al., Amer. J. Physiol. 282: F34,2002
Loop Diuretics
- Furosemide “Lasix”
- bumetanide “bumex”

Oral absorption
Readily Filtered
Secreted by the Proximal Tubule by “Organic acid transporter”
Inhibits Na:K:2Cl Cotransporter “NKCC”
- inhibits dilution and concentration of urine
- promote Ca and Mg excretion
- also cause vasodilation
Can cause volume depletion
  hypokalemia
  metabolic alkalosis
  hearing loss

Bartter’s Syndrome: a Genetic Disease resembling chronic Furosemide Use

- Chronic Volume depletion
- Hi renin, hi aldosterone
- hypokalemia
- metabolic alkalosis
- mutations in one of the following genes

NKCC  Na:K:2Cl Co-transporter
       Furosemide sensitive cotransporter
ROMK  K channel
CLC-Kb Chloride Channel
Sodium Absorption in Distal Tubule

TSC  Na:Cl Co-transporter
Thiazide sensitive cotransporter

Thiazide Diuretics
- Hydrochlorothiazide
- Chlorthiazide

Oral absorption
Readily Filtered
Secreted by organic anion transporter in Proximal Tubule
Inhibits NaCl cotransporter (TSC) in the distal tubule
- Increases delivery of NaCl out of the distal tubule
- Inhibits dilution but not concentration of urine
- Decreased calcium excretion

Can cause volume depletion
hypokalemia
glucose intolerance and hypercholesterolemia
?hyponatremia
**Gitelman’s Syndrome:** a genetic disease resembling chronic thiazide use

- mild volume depletion
- hypocalciuria
- hypomagnesiuria
- mutations in

**TSC**  Na:Cl Co-transporter
Thiazide sensitive cotransporter

**Cell Types of the Collecting Tubule**

<table>
<thead>
<tr>
<th>Principal</th>
<th>Na⁺ absorption</th>
<th>ENaC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water absorption</td>
<td>Aquaporin 2</td>
<td></td>
</tr>
<tr>
<td>K⁺ secretion</td>
<td>ROMK</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intercalated</th>
<th>H⁺ Transport</th>
<th>H⁺ ATPase</th>
</tr>
</thead>
</table>

![Cell Types Diagram](image)
Sodium Absorption in Collecting Duct

ENaC  Epithelial Na Channel
      Amiloride sensitive

K  K channel

Na Channel Blockers

- Amiloride
- Triamterene

Oral absorption
Readily Filtered
Inhibits the Epithelial Na channel
Reduces the lumen negative membrane potential which results in:
    inhibition of H⁺ secretion
    inhibition of K⁺ secretion

Can cause  hyperkalemia
Aldosterone Action in Collecting Duct

Binds to Mineralocorticoid Receptor **MR**
Increases opening of Na Channel **ENaC** and K channel
Increases activity of $H^+$ ATPase

Aldosterone Antagonists

*-Spironolactone*
*“Aldactone”*

Oral absorption
Readily Filtered
Competes with aldosterone for binding to its receptor
reduces activity of the Epithelial Na channel and $H^+$ ATPase
Reduces the lumen negative membrane potential which results in:
  - inhibition of $H^+$ secretion
  - inhibition of $K^+$ secretion
Can cause hyperkalemia
Complications of Diuretic Use
The complications are pharmacologic not idiosyncratic

Diuretics cause increased salt excretion and hence, their excessive use results in ECF Volume Depletion

Volume depletion causes increased renin, AII and Aldosterone which can lead to Hypokalemia, Metabolic Alkalosis and Hyperuricemia

Complications of Diuretic Use

Some diuretics have specific complications:

Acetazolamide can cause metabolic acidosis
Thiazides can cause hypercalcemia by increasing Ca reabsorption they occasionally cause hyperglycemia
Loop diuretics can cause hearing impairment they also increase calcium excretion in the urine
Amiloride can induce hyperkalemia
Resistance to Diuretics

Refactoriness

I. Decreased Delivery

- Excessive diuresis results in volume depletion causing high renin, AII and aldosterone

- High AII increases the Filtration Fraction and stimulates NaCl absorption in the proximal tubule thereby reducing the amount of Na delivered to the site of action of diuretics.
Driving Forces for Salt and Water Absorption in the Proximal Tubule

**Trans-cellular**  Active transport of Na and HCO$_3^-$

**Intercellular Leak**  Starling Forces across capillary  
($\Delta P - \Delta \Pi$)

Pathway of Salt and Water Absorption in the Proximal Tubule

**Net Flux** = **Trans-cellular** - **Leak**
Hypothetical Mechanism of the Effect of AII on Proximal Reabsorption

Volume Expansion

Volume Depletion

Resistance to Diuretics
Refractoriness

II. High Reabsorption

distal to the site of action of the diuretic
-Excessive diuresis results in volume depletion causing high renin, AII and aldosterone
-high aldosterone stimulates NaCl absorption in the collecting tubule thereby reabsorbing the Na that was destined for excretion as a consequence of the diuretic action
Mechanism of action of Vasopressin

Binds to V2 Receptor in collecting tubule
Increases production of cyclic AMP
Causes fusion of vesicles containing **Aquaporin 2** with the apical membrane
Aquaretics

- Vasopressin V2 Receptor antagonists
- Decrease production of cyclic AMP
- Inhibit fusion of Aquaporin 2 vesicles
- Allow dilute urine to be excreted