Urine Concentration and Dilution

Can vary from 30 mOsm (1/10 plasma P) to 1200 mOsm (4x plasma P).

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>50-130 mEq/L</td>
</tr>
<tr>
<td>K⁺</td>
<td>20-70 mEq/L</td>
</tr>
<tr>
<td>NH₄⁺</td>
<td>30-50 mEq/L</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>5-12 mEq/L</td>
</tr>
<tr>
<td>Mg²⁺</td>
<td>2-18 mEq/L</td>
</tr>
<tr>
<td>Cl⁻</td>
<td>50-130 mEq/L</td>
</tr>
<tr>
<td>P₁</td>
<td>20-40 mEq/L</td>
</tr>
<tr>
<td>pH</td>
<td>5-7</td>
</tr>
</tbody>
</table>

Waste Products

Urea              | 200-400 mM       |
Creatinine        | 6-20 mM          |

Osmolality        | 500-800 mOsm/Kg H₂O |

Relative osmolality of the tubule fluid along the nephron.
Generating a Hyperosmotic Medulla and Urine

Have to know:

✓ The solute and water permeability characteristics of each tubule section.

✓ The osmotic gradient between the tubule lumen and the surrounding interstitium.

✓ The transport mechanisms between that generate the hyperosmotic medullary interstitium.

✓ The exchange mechanisms that act among the tubules, interstitium and blood vessels to maintain the hyperosmotic medullary.

Solute concentration in the medulla is generated by:

✓ Active reabsorption of NaCl in the thick ascending limb.
✓ Osmosis out of the thin descending limb into the interstitium.
✓ Flow of fluid through the nephron.
The overall idea behind the loop of Henle is:

1. the thick ascending limb adds solutes (but no water) to the interstitial space via active transport (mostly NaCl).
2. the addition of solutes into the interstitial space draws water from the nephron lumen in the thin descending limb concentrating solutes in the nephron lumen.
3. flow down the nephron brings the concentrated solutes from the thin descending limb to the thick ascending limb where active transport can move even more solutes into the interstitial space.

Thus there is a positive feedback loop that results in more and more transport of NaCl into the interstitial space.

The loop of Henle concentrates solutes in the interstitial space. The filtrate (to be urine) leaving the loop of Henle has not be concentrated. It is either isosmotic or hyposmotic to plasma.
Nephron Permeability to Urea

Most of the nephron segments are relatively impermeable to urea. As the filtrate flows down the nephron towards the collecting ducts water is reabsorbed and the lumen concentration of urea increases. The urea concentration is highest in the collecting ducts. The permeability to urea in the collecting ducts is sensitive to anti-diuretic hormone (ADH, see next few slides). An increase in the plasma concentration of ADH will increase the number of urea channels.

Urea Recirculation

1. urea diffuses down its concentration gradient from the collecting ducts into the medullary interstitial space ($P_{\text{urea}}$ in collecting ducts is high).
2. urea diffuses down its concentration gradient from the interstitial space into the lumen of the loop of Henle ($P_{\text{urea}}$ in loop of Henle is medium)
3. nephron flow brings urea back to the collecting ducts
The vasa recta helps to preserve the medullary osmotic gradient. It minimizes washout of the medullary concentrates.
### OBLIGATORY URINE VOLUME

<table>
<thead>
<tr>
<th>70 kg adult must excrete</th>
<th>600 mosmoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>maximum urine concentration</td>
<td>1200 mosmoles/L</td>
</tr>
<tr>
<td>minimum urine volume</td>
<td>( \frac{600 \text{ mosmoles}}{1200 \text{ mosmoles/L}} = 0.5 \text{ Liters} )</td>
</tr>
</tbody>
</table>

### INGESTION OF SALT WATER

<table>
<thead>
<tr>
<th>1 Liter salt water</th>
<th>2400 mOsmoles</th>
</tr>
</thead>
<tbody>
<tr>
<td>To excrete 2400 mosmoles, need</td>
<td>( \frac{2400 \text{ mosmoles}}{1200 \text{ mosmoles/L}} = 2 \text{ Liters} )</td>
</tr>
</tbody>
</table>

For every 1 liter salt water, need to excrete 2 liters \( \rightarrow \) dehydration

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**Relative osmolality of the tubule fluid along the nephron.**

- **Proximal tubule**
- **Loop**
- **Cortical collecting tubule (CCT)**
- **Medullary collecting ducts (OMCD, IMCD)**

[Graph showing osmolality changes along the nephron]
Water permeability in different nephron segments.
Cellular mechanism of arginine vasopressin (AVP) action in the collecting tubules and ducts.
The kidneys increase Na⁺ excretion in response to increases in extracellular fluid volume, not an increase in extracellular fluid concentration.

# Effect of Abrupt Changes in Na⁺ Intake

**A**

- **Weight (kg)**
  - 60
  - 70
  - 80
  - 90
  - 100
- **Na⁺ (mEq/d)**
  - 50
  - 100
  - 150
  - 200
- **Output**
- **Positive balance**
- **Negative balance**
- **Days**
  - 1
  - 2
  - 7
  - 11

# Effect of Positive Na⁺ Balance on Na⁺ Excretion

**B**

- **Gain in extracellular water (l)**
- **0**
- **200**
- **400**
- **600**
- **800**
- **1000**
- **1200**
- **Amount of Na⁺ retained by body**
- **0**
- **200**
- **400**
- **600**
- **800**
- **1000**
- **1200**

**Feedback control of ECV**

- Increased renal Na⁺ retention: contractile decreased effective circulating volume

- Effective circulating volume

- Cardiac output

- Arterial pressure

- Renal blood flow (RBF)

- Angiotensin II (ANG II)

- Aldosterone

- Angiotensin-converting enzyme (ACE)

- Brainstem: pituitary, parasympathetic nervous system, sympathetic nervous system, hypothalamus, vasopressin, renin

- Changes in hemodynamics and tubular transport

- Na⁺ excretion
Macula Densa

A set of cells in the early part of the distal tubule. These epithelial cells can sense changes in the filtrate volume delivered to the distal tubule (mechanism not completely worked out, but see next slide for details). These epithelial cells are thought to secrete paracrine substances which influence the neighboring afferent and efferent arterioles.

Afferent/Efferent arterioles

Constriction or dilation of smooth muscle cells surrounding the arterioles alters renal blood flow and also impacts the glomerular filtration rate.

TUBULOGLomerular FEEDBACK MECHANISM

↑ P_Arterial → ↑ P_Glomerulus → RBF → GFR

↓ FLUID FLOW THROUGH NEPRHON

↓ FLUID FLOW PAST MACULA DENSA

↑ RELEASE OF VASOCONSTRICTOR

↓ CONTRACTION OF AFFERENT ARTERIOLE
The renin-angiotensin-aldosterone axis.

Renin release from granular cells is affected by:

- ↑ Sympathetic input from central baroreceptors.
- ↓ Renal perfusion pressure → ↓ flow past macula densa
Actions of Angiotensin II

- Stimulation of aldosterone from the adrenal cortex
- Vasoconstriction of renal and other systemic vessels
- Enhances tubuloglomerular feedback
- Enhances Na-H exchange in the proximal tubule and thick ascending limb (increases Na\(^+\) and water reabsorption).
- Hypertrophy of renal tubule cells
- Stimulated thirst and AVP release

Hemodynamic Actions of Angiotensin II
RENIN-ANGIOTENSIN SYSTEM: CONTROL OF PRESSURE

↓ Arterial Pressure/ Blood Volume

↑ RENIN SECRETION

↑ ANGIOTENSIN II

↑ Total peripheral resistance

↑ Na⁺, H₂O REABSORPTION

Renin-angiotensin II negative feedback loop

1. A decrease in blood pressure or volume stimulates renin release.
2. Renin release leads to an increase in total peripheral resistance and an increase in sodium and water reabsorption.
3. This leads to an increase in blood pressure or volume which compensates for the

A GENOMIC EFFECTS OF ALDOSTERONE ON Na⁺ TRANSPORT

Average number of open Na⁺ channels (NPC)

Plasma aldosterone (ng/dL)

The Aldo-MR complex stimulates transcription.

Proteins and mRNA

EMC2 Na⁺ channels

Mitochondria

Principal cell of cortical collecting tubule

Blood

Mineralocorticoid receptor

Interstitial space

Aldrosterone/ MR complex

3 Na⁺

K⁺
Atrial natriuretic hormone promotes Na⁺ and water excretion.

- GFR is increased.
- Na⁺ reabsorption is inhibited.
- Thiazide-sensitive Na⁺ reabsorption is inhibited.
- Sodium excretion is increased.
- Potassium excretion is decreased.
- Hypertonicity of the medullary interstitium is decreased.
- Urinary Na⁺ excretion is increased.
Dependence of arginine vasopressin (AVP) release on plasma osmolality.

Atrial natriuretic peptide is released by atrial cells in response to volume changes. An increase in volume results in an increase the release of atrial natriuretic peptides which has four effects:

1. a decrease in sodium and water reabsorption in the collecting ducts.
2. an increase in the glomerular filtration rate, via vasodilation of the afferent arteriole and vasoconstriction of the efferent arteriole.
3. inhibition of renin release
4. inhibition of ADH release

All four result in an increase in the amount of sodium and water excreted by the kidneys.
Control of arginine vasopressin (AVP) synthesis and release by osmoreceptors.

F. HORMONES AND SMALL MOLECULES

A number of hormones and small molecules influence both renal resistances and sodium and water reabsorption.

Hormones that alter reabsorption:

<table>
<thead>
<tr>
<th>HORMONE</th>
<th>SITE OF ACTION</th>
<th>EFFECT (on Na+/H2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>PT</td>
<td>↑ NaCl, H2O reabsorption</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>DT/CD</td>
<td>↑ NaCl, H2O reabsorption</td>
</tr>
<tr>
<td>Atrial natriuretic peptide</td>
<td>CD</td>
<td>↑ NaCl, H2O reabsorption</td>
</tr>
<tr>
<td>Antidiuretic Hormone</td>
<td>DT/CD</td>
<td>↑ H2O reabsorption</td>
</tr>
</tbody>
</table>

Hormones that alter blood vessel diameter

<table>
<thead>
<tr>
<th>Vasoconstrictors</th>
<th>STIMULUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin II</td>
<td>↓ volume, pressure</td>
</tr>
<tr>
<td>Endothelin</td>
<td>↑ stretch, angiotensin II, bradykinin, epinephrine, volume</td>
</tr>
<tr>
<td>Adenosine</td>
<td>tubuloglomerular feedback?</td>
</tr>
<tr>
<td>ATP</td>
<td>↑ volume</td>
</tr>
<tr>
<td>ANP</td>
<td>↑ volume</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vasodilators</th>
<th>STIMULUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostaglandins (PGE1, PGE2)</td>
<td>↓ volume, ↑ stretch, angiotensin II</td>
</tr>
<tr>
<td>Nitric oxide (NO)</td>
<td>↑ stretch, acetylcholine, histamine, bradykinin, ATP</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>prostaglandins, ↓ACE</td>
</tr>
<tr>
<td>Histamine</td>
<td></td>
</tr>
<tr>
<td>Dopamine</td>
<td></td>
</tr>
<tr>
<td>ATP</td>
<td></td>
</tr>
<tr>
<td>ANP</td>
<td></td>
</tr>
</tbody>
</table>

↑ volume