Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

- **Public Domain – Government**: Works that are produced by the U.S. Government. (17 USC § 105)
- **Public Domain – Expired**: Works that are no longer protected due to an expired copyright term.
- **Public Domain – Self Dedicated**: Works that a copyright holder has dedicated to the public domain.
- **Creative Commons – Zero Waiver**
- **Creative Commons – Attribution License**
- **Creative Commons – Attribution Share Alike License**
- **Creative Commons – Attribution Noncommercial License**
- **Creative Commons – Attribution Noncommercial Share Alike License**
- **GNU – Free Documentation License**

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

- **Public Domain – Ineligible**: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ*

{ Content Open.Michigan has used under a Fair Use determination. }

- **Fair Use**: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ*
  
  Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we **DO NOT** guarantee that your use of the content is Fair.
  
  To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.
Physiology of Water Metabolism

Michael Heung, M.D.
M2 Renal Sequence
Objectives

• Distinguish between solute and free water clearance
• Understand the differential transport of water and electrolytes in the renal tubules
• Understand countercurrent multiplication and its role in urinary concentration
• Know the regulation of ADH release and its effects on water reabsorption
• Be familiar with the aquaporin family of proteins
• Understand the role of thirst in maintaining water balance
<table>
<thead>
<tr>
<th></th>
<th>Osmoregulation</th>
<th>Volume regulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Signal</strong></td>
<td>Plasma osmolality</td>
<td>“Effective” circulating volume</td>
</tr>
<tr>
<td><strong>Sensors</strong></td>
<td>Hypothalamic osmoreceptors</td>
<td>Carotid sinus, large vein, atrial, and intrarenal receptors</td>
</tr>
<tr>
<td><strong>Effectors</strong></td>
<td>ADH, thirst</td>
<td>Renin/angiotensin, aldosterone, sympathetic nerves, ANP, ADH</td>
</tr>
<tr>
<td><strong>Observed responses</strong></td>
<td>Urine osmolality, water intake</td>
<td>Urinary sodium excretion</td>
</tr>
</tbody>
</table>
## Typical Daily Water Balance

<table>
<thead>
<tr>
<th>Source</th>
<th>Water intake (ml/day)</th>
<th>Source</th>
<th>Water output (ml/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingested water</td>
<td>1400</td>
<td>Urine</td>
<td>1500</td>
</tr>
<tr>
<td>Water content of food</td>
<td>850</td>
<td>Skin</td>
<td>500</td>
</tr>
</tbody>
</table>
| Water of oxidation            | 350                   | Respiratory tract | 400  
  Stool                      |                       | Stool           | 200                   |
| Total:                        | 2600                  | Total:          | 2600                  |
## Daily Renal Resorptive Workload

<table>
<thead>
<tr>
<th>Substance</th>
<th>Filtered</th>
<th>Excreted</th>
<th>Reabsorbed</th>
<th>% net reabsorbed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water (L)</td>
<td>180</td>
<td>1.5</td>
<td>178.5</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Sodium (mEq)</td>
<td>25,200</td>
<td>150</td>
<td>25,050</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Chloride (mEq)</td>
<td>18,000</td>
<td>150</td>
<td>17,850</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Bicarbonate (mEq)</td>
<td>4320</td>
<td>2</td>
<td>4318</td>
<td>&gt;99</td>
</tr>
<tr>
<td>Potassium (mEq)</td>
<td>720</td>
<td>100</td>
<td>620</td>
<td>&gt;85</td>
</tr>
<tr>
<td>Calcium (mEq)</td>
<td>540</td>
<td>10</td>
<td>530</td>
<td>&gt;98</td>
</tr>
<tr>
<td>Urea (g)</td>
<td>56</td>
<td>28</td>
<td>28</td>
<td>50</td>
</tr>
<tr>
<td>Glucose (mmol)</td>
<td>800</td>
<td>0</td>
<td>800</td>
<td>100</td>
</tr>
</tbody>
</table>
# Solute vs. Water Clearance

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{Osm}$</td>
<td>300 mOsm/kg water</td>
<td>300 mOsm/kg water</td>
<td>300 mOsm/kg water</td>
</tr>
<tr>
<td>$U_{Osm}$</td>
<td>300 mOsm/kg water</td>
<td>150 mOsm/kg water</td>
<td>600 mOsm/kg water</td>
</tr>
<tr>
<td>Urine flow (ml/min)</td>
<td>2 mL/min</td>
<td>4 mL/min</td>
<td>1 mL/min</td>
</tr>
</tbody>
</table>

- What is each patient’s solute clearance?
- What is each patient’s water balance?
Free Water Clearance

- Clearance_{osm} = (U_{osm} \times V) / P_{osm}

  **Patient 1:**  \( C_{Osm} = (300 \times 2)/300 = 2 \text{ mL/min} \)
  Urine flow 2mL/min → *Even water balance*

  **Patient 2:**  \( C_{Osm} = (150 \times 4)/300 = 2 \text{ mL/min} \)
  Urine flow 4mL/min → *Free water excretion*

  **Patient 3:**  \( C_{Osm} = (600 \times 1)/300 = 2 \text{ mL/min} \)
  Urine flow 1mL/min → *Free water retention*

- *Solute clearance is identical, but water clearance is divergent*
Renal Water Handling

- For renal excretion to vary between filtered substances, there must be differential transport within the tubular epithelium.

- Although there is overlap, water and sodium handling are independently regulated.
Proximal Tubule

- 67% of filtered load
- Sodium and water are absorbed iso-osmotically
- Water flow is passive and follows the osmotic gradient established by Na reabsorption
Loop of Henle

• Descending thin limb
  – 15% of filtered load
  – Passive reabsorption

• Thick ascending limb
  – Impermeable to water
  – Diluting segment
Distal Tubule and Collecting Duct

- Early DT is water impermeable: further urinary dilution
- Late DT and CD account for 8-17% of filtered load
  - Permeability is ADH dependent
Summary:
Tubular Water Permeability

** ADH is the most important regulator of water balance
Final Urinary Concentration

- Concentration is dependent on:
  1. Interstitial gradient
  2. ADH effect

- Maximal concentration ~1200 mOsm/kg water
- Minimal concentration ~50 mOsm/kg water
Why Do Our Nephrons Have Loops?

- Freshwater fishes
  - Glomerulus, proximal and distal tubules
  - $U/P_{OSM} = 0.1$

- Amphibians
  - Smaller glomerular capillary tuft
  - $U/P_{OSM} = 0.2 - 0.9$

- Mammals
  - Loop of Henle
  - $U/P_{OSM} = 0.17 - 4$

Source Undetermined
Countercurrent Multiplication: Establishing An Osmotic Gradient

- Active Na transport in ascending limb
- Passive water reabsorption in descending limb
ADH Regulation

**Primary stimuli:**

1. **Osmolality**
   - Hypothalamic osmoreceptors
   - Sensitive (1%)
   - Setpoint

2. **Hemodynamic**
   - Baroreceptors
   - Insensitive (5-10%) but overriding
ADH Actions

• 2 main stimuli, 2 different receptors (and 2 names!)

“vasopressin”
ADH Set Point: Variation with Volume/Pressure

- Can also be altered in pregnancy, cancer, psychosis
Effect of ADH on Tubular Fluid Osmolality

<table>
<thead>
<tr>
<th>Nephron segment</th>
<th>No ADH</th>
<th>Max ADH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal tubule</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Start of descending thin limb</td>
<td>300</td>
<td>300</td>
</tr>
<tr>
<td>Start of ascending thin limb</td>
<td>1200</td>
<td>1200</td>
</tr>
<tr>
<td>End of TAL</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>End of cortical collecting duct</td>
<td>50-100</td>
<td>300</td>
</tr>
<tr>
<td>Final urine</td>
<td>50</td>
<td>1200</td>
</tr>
</tbody>
</table>

The most important measure of ADH effect is urine osmolality.
The Aquaporin Family

- AQP1
- AQP2
- AQP3
- AQP4
- AQP6
- AQP7
- AQP8

Source Undetermined
Aquaporin 2

- Stored in intracellular vesicles in collecting duct epithelium
- Through cAMP-mediated signaling, vesicles move to apical membrane
- In absence of ADH, water channels are re-internalized
Summary: Water Transport During Diuresis and Anti-Diuresis
Defining Oliguria

Oliguria: the minimal required urine output to excrete the daily obligate solute load (eg. Na ingestion, protein metabolism)

An average obligate waste solute load is 600 mosm/day. The kidneys’ maximal urinary concentration is 1200 mosm/kg H₂O.

Excretion = urine volume x [waste]

- What is the minimal amount of water clearance (i.e. urine output) to excrete the daily waste load?
  \[
  \frac{600\text{mosm/day}}{1200\text{mosm/kg H}_2\text{O}} = 0.5\text{kg H}_2\text{O/day} \\
  = 500\text{mL/day}
  \]

- What would be the minimal amount of urine output if we could only concentrate our urine to 300mosm/kg H₂O?
  \[
  \frac{600\text{mosm/day}}{300\text{mosm/kg H}_2\text{O}} = 2000\text{mL/day}
  \]
Is there a *maximal* urine output?

Rule: You can’t pee pure water!

An average obligate waste solute load is 600 mosm/day. The kidneys’ maximal urinary dilution is 50 mosm/kg $H_2O$.

Excretion = urine volume x [waste]

What is the maximal amount of urine that can be produced?

$$\frac{600\text{mosm/day}}{50\text{mosm/kg} \ H_2O} = 12\text{kg} \ H_2O/\text{day}$$

= 12L/day urine output

What happens if you drink more than 12L of water in a day?

*Water intoxication* $\rightarrow$ *hyponatremia*
Regulating Water Ingestion

- Excess water ingestion is managed by increased renal free water excretion

- Free water depletion is managed by both increased renal water reabsorption and water ingestion

- An intact thirst mechanism alone can prevent the development of significant free water depletion

- Thirst mechanism: 1. Thirst sensation
  2. Access to water
Thirst

- Regulated by hypothalamic receptors:
  - Subfornical organ
  - Organum vasculosum

- Signals: 1. Osmolality
  - 2. Hemodynamic sensing
    - Independent from (but synergistic with) ADH secretion
    - Also stimulated by angiotensin II

- Receptors in oropharynx and upper GI tract sense water intake
  - Relief even before correction of osmolality
Questions?