Urine Concentration and Dilution; Regulation of Extracellular Fluid Osmolarity and Sodium Concentration. Chapter 28

Yanal A. Shafagoj MD. PhD
One of the most important tests is to look if the kidney can concentrate urine which is considered to be a tubular function

- Urine specific gravity test (it tests the ability of the kidneys to concentrate urine)
  - High specific gravity means concentrated urine
  - Low specific gravity means diluted urine
  - This is the last function to be retained following acute renal failure
Concentration and Dilution of the Urine

• Maximal urine concentration
  \[ = 1200 - 1400 \text{ mOsm/L} \]
  (specific gravity \( \sim 1.030 \))

• Minimal urine concentration
  \[ = 50 - 70 \text{ mOsm/L} \]
  (specific gravity \( \sim 1.003 \))
Relationship between urine osmolarity and specific gravity

Influenced by:
- glucose in urine
- protein in urine
- antibiotics
- radiocontrast media
Making concentrated urine means conservation of body water.

- Making diluted urine mean eliminating excess water.

**Observation:**

- Only those species that have juxtamedullary nephrons (long loop of Henle) can make concentrated urine (desert rodents). While beaver with short loop of Henle make less concentrated urine
To make diluted urine is somehow easy to understand. The kidneys need to actively transport NaCl at the collecting duct and end up with diluted urine=hypo-osmolar urine.

To make concentrated urine was an enigma for 100 years (Active transport of water is not known). The micropuncture technique came up with the answer. Using the micropuncture technique scientists measured the osmolarity of inner medullary interstitium and found to be hyperosmolar.
Before we start the lecture, we ask the following question: Why we must drink water?

- Normally, we must excrete 700 mOsm/day as a minimum amount (in a complete bed rest individual), or 1000 mOsm/D at normal daily activity.
- The kidney can make a concentrated urine up to 1400 mOsm/l.
- Therefore, 0.5 l is the minimum daily obligatory volume of urine (MDOVU): $\frac{700}{1400}$ or 714 ml $\frac{1000}{1400}$ during normal daily activity.
- MDOVU is:
  - Infants $< 1$ ml/kg/h
  - Children $< 0.5$ ml/kg/h
  - Adults $< 0.3$ ml/kg/h
- In general MDOVU = 300ml$m^2$ BSA/D.
# Water Balance

<table>
<thead>
<tr>
<th></th>
<th>Intake</th>
<th>Output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Metabolism 200 ml</td>
<td>GIT 100 ml</td>
</tr>
<tr>
<td>2.</td>
<td>Drinking 1600 ml</td>
<td>Skin 600 ml</td>
</tr>
<tr>
<td>3.</td>
<td>Food 700 ml</td>
<td>Respiratory 300 ml</td>
</tr>
<tr>
<td>4.</td>
<td></td>
<td>Urine 1500</td>
</tr>
<tr>
<td></td>
<td>2500</td>
<td>2500</td>
</tr>
</tbody>
</table>
In order to form Concentrated Urine, two conditions must be met:

1. Hyperosmolar interstitium around the medullary collecting ducts
2. ADH to permit $H_2O$ permeability.
How to generate hyperosmolar interstitium?

By the so called “single effect”. In thick ascending loop of Henle, Na\(^+\)-K\(^+\)-2Cl\(^-\) transporter without H2O reabsorption, making interstitium hyperosmolar with 700 mOsm/L

- The rest is made by urea
- Na\(^+\) that is reabsorbed must not be removed from the area, and therefore blood flow in Vasa Recta must be low (2% of renal blood flow). High blood flow does not allow this hyperosmolar media to build up.
ADH

- Both ADH and oxytocin are composed of 9 aa (small peptides)
- ADH: 5/6th from supraoptic nuclei and 1/6th from paraventricular nuclei.
- ADH → V2 receptor (AQP V2) → cAMP → intracellular vesicles → aquaporins → in luminal side (takes 5-10 min).
- AQP V3 and V4 do not respond to ADH.
- ADH receptors are found in last one third of DT and further.
- **Functions of ADH:**
  1. ↑ H₂O reabsorption from last one third of DT and further.
  2. Enhances active NaCl reabsorption from last one third of DT and further.
  3. Enhances urea reabsorption from IMCD.
- The last two factors make medulla hyperosmolar.
Control of Extracellular Osmolarity (NaCl Concentration)

- ADH
- Thirst

ADH -Thirst Osmoreceptor System

Mechanism:

increased extracellular osmolarity (NaCl) stimulates ADH release, which increases H$_2$O reabsorption, and stimulates thirst (intake of water)
Water diuresis in a human after ingestion of 1 liter of water.
Formation of a dilute urine

- Continue electrolyte reabsorption
- Decrease water reabsorption

**Mechanism:**
- Decreased ADH release
- Reduced water permeability in distal and collecting tubules

[Diagram showing the process of formation of a dilute urine with electrolyte and water reabsorption.]
Formation of a Concentrated Urine

• Continue electrolyte reabsorption
• Increase water reabsorption

Mechanism:
• Increased ADH release which increases water permeability in distal and collecting tubules
• High osmolarity of renal medulla
• Countercurrent flow of tubular fluid
Formation of a Concentrated Urine when antidiuretic hormone (ADH) are high.
Obligatory Urine Volume

Again: The minimum urine volume in which the excreted solute can be dissolved and excreted

Example:
If the max. urine osmolarity is 1400 mOsm/L, and 700 mOsm of solute must be excreted each day to maintain electrolyte balance, the obligatory urine volume is:

\[
\frac{700 \text{ mOsm/d}}{1400 \text{ mOsm/L}} = 0.5 \text{ L/day}
\]
Obligatory Urine Volume

In renal disease the obligatory urine volume may be increased due to impaired urine concentrating ability.

Example:
- If the max. urine osmolarity = 300 mOsm/L,
- If 700 mOsm of solute must be excreted each day to maintain electrolyte balance
- obligatory urine volume = ?

\[
\frac{700 \text{ mOsm/d}}{300 \text{ mOsm/L}} = 2.3 \text{L/day}
\]
Factors That Contribute to Buildup of Solute in Renal Medulla - Countercurrent Multiplier

- Active transport of Na\(^+\), Cl\(^-\), K\(^+\) and other ions from thick ascending loop of Henle into medullary interstitium
- Active transport of ions from medullary collecting ducts into interstitium
- Passive diffusion of urea from medullary collecting ducts into interstitium
- Diffusion of only small amounts of water into medullary interstitium
## Summary of Tubule Characteristics

<table>
<thead>
<tr>
<th>Tubule Segment</th>
<th>Active NaCl Transport</th>
<th>Permeability</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H₂O</td>
<td>NaCl</td>
</tr>
<tr>
<td>Proximal</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Thin Desc.</td>
<td>0</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Thin Ascen.</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Thick Ascen.</td>
<td>+++</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Distal</td>
<td>+</td>
<td>+ADH</td>
<td>0</td>
</tr>
<tr>
<td>Cortical Coll.</td>
<td>+</td>
<td>+ADH</td>
<td>0</td>
</tr>
<tr>
<td>Inner Medullary Coll.</td>
<td>+</td>
<td>+ADH</td>
<td>0</td>
</tr>
</tbody>
</table>
Countercurrent multiplier system in the loop of Henle.

Figure 28-4
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Net Effects of Countercurrent Multiplier

1. More solute than water is added to the renal medulla. i.e. solutes are “trapped” in the renal medulla.
2. Fluid in the ascending loop is diluted.
3. Most of the water reabsorption occurs in the cortex (i.e. in the proximal tubule and in the distal convoluted tubule) rather than in the medulla.
4. Horizontal gradient of solute concentration established by the active pumping of NaCl is “multiplied” by countercurrent flow of fluid.
Recirculation of urea absorbed from medullary collecting duct into interstitial fluid.
Urea recycling

- Urea toxic at high levels, but can be useful in small amounts.
- Urea recycling causes buildup of high [urea] in inner medulla.
- This helps create the osmotic gradient at loop of Henle so H₂O can be reabsorbed.
Urea Recirculation

• Urea is passively reabsorbed in proximal tubule (~ 50% of filtered load is reabsorbed)
• In the presence of ADH, water is reabsorbed in distal and collecting tubules, concentrating urea in these parts of the nephron
• The inner medullary collecting tubule is highly permeable to urea, which diffuses into the medullary interstitium
• ADH increases urea permeability of medullary collecting tubule by activating urea transporters (UT-1)
The Vasa Recta Preserve Hyperosmolarity of Renal Medulla

- The vasa recta serve as countercurrent exchangers

- Vasa recta blood flow is low (only 1-2% of total renal blood flow)
Changes in osmolarity of the tubular fluid

Figure 28-8
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Summary of water reabsorption and osmolarity in different parts of the tubule

- Proximal Tubule: 65% reabsorption, isosmotic
- Desc. loop: 15% reabsorption, osmolarity increases
- Asc. loop: 0% reabsorption, osmolarity decreases
- Early distal: 0% reabsorption, osmolarity decreases
- Late distal and coll. tubules: ADH dependent water reabsorption and tubular osmolarity
- Medullary coll. ducts: ADH dependent water reabsorption and tubular osmolarity
“Free” Water Clearance ($C_{H2O}$)  
(rate of solute-free water excretion)

$$CH_2O = V - \frac{Uosm \times V}{Posm}$$

where:

$Uosm = $ urine osmolarity

$V = $ urine flow rate

$P = $ plasma osmolarity

If: $Uosm < Posm$, $C_{H2O} = +$

If: $Uosm > Posm$, $CH2O = -$
Given the following data, calculate "free water" clearance:

- urine flow rate = 6.0 ml/min
- urine osmolarity = 150 mOsm /L
- plasma osmolarity = 300 mOsm /L

Is free water clearance in this example positive or negative?
Answer

\[
\text{CH}_2\text{O} = V - \frac{\text{Uosm} \times V}{\text{Posm}}
\]

\[
= 6.0 - \frac{(150 \times 6)}{300}
\]

\[
= 6.0 - 3.0
\]

\[
= +3.0 \text{ ml / min (positive)}
\]
Disorders of Urine Concentrating Ability

• Failure to produce ADH:
  “Central” diabetes insipidus

• Failure to respond to ADH:
  “nephrogenic” diabetes insipidus
  - impaired loop NaCl reabs. (loop diuretics)
  - drug induced renal damage: lithium, analgesics
  - malnutrition (decreased urea concentration)
  - kidney disease: pyelonephritis, hydronephrosis, chronic renal failure
Development of Isosthenuria With Nephron Loss in Chronic Renal Failure (inability to concentrate or dilute the urine)

![Graph showing the relationship between osmolarity and nephron loss.](image-url)
# Total Renal Excretion and Excretion Per Nephron in Renal Failure

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>75% loss of nephrons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nephrons</td>
<td>2,000,000</td>
<td>500,000</td>
</tr>
<tr>
<td>Total GFR (ml/min)</td>
<td>125</td>
<td>40</td>
</tr>
<tr>
<td>GFR per nephron (nl/min)</td>
<td>62.5</td>
<td>80</td>
</tr>
<tr>
<td>Total Urine flow rate (ml/min)</td>
<td>1.5</td>
<td>1.5</td>
</tr>
<tr>
<td>Volume excreted</td>
<td>0.75</td>
<td>3.0</td>
</tr>
<tr>
<td>per nephron (nl/min)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Osmoreceptor—antidiuretic hormone (ADH) feedback mechanism for regulating extracellular fluid osmolarity.
ADH synthesis in the magnocellular neurons of hypothalamus, release by the posterior pituitary, and action on the kidneys
Stimuli for ADH Secretion

- Increased osmolarity
- Decreased blood volume (cardiopulmonary reflexes)
- Decreased blood pressure (arterial baroreceptors)
- Other stimuli:
  - input from cerebral cortex (e.g. fear)
  - angiotensin II
  - nausea
  - nicotine
  - morphine
ADH is released upon:
1. Increased osmolarity (Osmoreceptors in hypothalamus). An increase of 1% (2-3 mOsm/l) is enough to stimulate ADH secretion.
2. Decreased blood pressure (arterial baroreceptor reflex (high-pressure regions such as aortic and carotid sinus, and low-pressure regions such as cardiac atria and cardiopulmonary reflexes),
3. Decreased blood volume. We need a decrease of blood volume by 10% to stimulate ADH release.
The effect of increased plasma osmolarity or decreased blood volume.
Factors That Decrease ADH Secretion

- Decreased osmolarity
- Increased blood volume (cardiopulmonary reflexes)
- Increased blood pressure (arterial baroreceptors)
- Other factors:
  - alcohol
  - clonidine (antihypertensive drug)
  - haloperidol (antipsychotic, Tourette’s)
Stimuli for Thirst

- Increased osmolarity
- Decreased blood volume (cardiopulmonary reflexes)
- Decreased blood pressure (arterial baroreceptors)
- Increased angiotensin II
- Other stimuli:
  - dryness of mouth
Factors That Decrease Thirst

- Decreased osmolarity
- Increased blood volume
  (cardiopulmonary reflexes)
- Increased blood pressure
  (arterial baroreceptors)
- Decreased angiotensin II
- Other stimuli:
  - Gastric distention
Effect of Changes in Sodium Intake on Plasma Sodium After Blocking ADH-Thirst System

Plasma Sodium Conc. (mEq/L)

Sodium Intake (mEq/day)
Effect of Changes in Sodium Intake on Plasma Sodium After Blocking Aldosterone or Ang II System

Plasma Sodium Conc. (mEq/L)

Sodium Intake (mEq/day)

normal

aldosterone system blocked

Ang II Blocked