Osmoregulation and volume regulation

Learning objectives: 78, 79

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Normal values connected to these topics

• urine osmotic concentration: 70-1200 mosmol/L
• urine specific gravity: 1001-1030 g/l
• (blood plasma 1012 g/l)
• diuresis and its interpretation: <100 ml/day: anuria; 100-600 ml/day: oliguria, 600-2500 ml/day: normal range, >2500 ml/day: polyuria, in diabetes insipidus can reach 18-25 l/day!
• minimal daily excreted osmotic activity: 650 mosmol
• Na⁺ dietary intake/loss: 100-400 mmol/day, this corresponds with 5-30 g table salt consumption
Water household

**Water intake**
- Fluid intake: 1000-2000 ml/day
- Water content of foodstuffs: 800-1000 ml/day
- Oxidative water: 300-400 ml/day

**Water output**
- Insensible perspiration: 800-1000 ml/day
- Sensible perspiration, sweating: 200 ml/day
- Stool: 100-200 ml/day
- Urine: 1000-2000 ml/day

*Minimal urine output 500-600 ml/day (650 mosm solute/day).*

- **Physiology of thirst**
  1. dryness of the mouth
  2. angiotensin II
  3. hypothalamic osmoreceptors
Control of water intake (hyperosmosis and hypovolaemy)

Regulation of vasopressin (AVP) production

Renin-angiotensin system stimulates Atrial Natriuretic Hormon inhibits the AVP production.
Effects of AVP:

- Water reabsorption from the collecting duct through Aquaporin-2 water channels (V2/cAMP)

- V1/ITP-Ca²⁺ vasoconstrictor effect

- V3 receptor in the ACTH producing neurons of the anterior pituitary gland
The water transport of the distal nephron is regulated by the anti-diuretic hormone (ADH).

The collecting duct is relatively impermeable to water and urea in the absence of ADH.

In the presence of ADH the water permeability of the whole collecting duct and the urea permeability of its papillary part is greatly increasing.
In the absence of ADH the osmolality of the fluid that leaves the collecting duct is 70 mosm/kg (50 mosm/kg urea and 20 mosm/kg electrolyte).

In the absence of ADH or V2 ADH receptor up to 15% of the filtrated water will be excreted (max. 26 liter/day) diabetes insipidus.

<table>
<thead>
<tr>
<th>ADH secretion</th>
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<td><strong>Increased by</strong></td>
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<td>1. High osmolarity of the blood</td>
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<td>2. Hypovolemia (inhibits ANP secretion)</td>
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<td>3. Standing ↓<strong>ANP</strong>↓</td>
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<td>4. venous stasis</td>
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<td>5. pain, exercise</td>
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The osmolarity of the tubular fluid

Depending on the need of the body the kidney can produce

1. highly concentrated (to 1.200 mOsm/l) or
2. strongly diluted urin (to 70 mOsm/l).
Factors influencing urine concentration:
Length of Henle loops
Percentage of long-looped nephrons compared to short-looped ones
Urea
Flow through Henle-loop and collecting duct
Blood-flow through vasa recta
Prostaglandines (PGE₂, PGD₂)

Concentration and Dilution of Urine

Countercurrent multiplication

Medullary gradient

300 mosm/kg-1200 mosm/kg
Horisontal gradient – Active Na\(^+\) reabsorption in the ascending thick segment of the loop of Henle

Vertical gradient (countercurrent) - Fluid movement in the descending and ascending segment of the Henle-loop

Loop diuretics (i.e. Furosemide) abolishe the medullary gradient

**The motor of the concentrating of the urin is the electrolyt transport in the loop of Henle**

The most important function of the loop of Henle is the bilding of hyperosmolar renal medulla. The ascending thick segment resorbs actively Na and Cl, practically without water resorption. These transports decrease the osmolarity of the tubular fluid and increase the osmolarity in the renal medulla.
Urea transport in the nephron

Urea-cycle

CORTEX

OUTER ZONE

INNER ZONE

MEDULLA

ACTIVE TRANSPORT

PASSIVE TRANSPORT

Urea amount

urea concentration (mmol)

Gerrig Themen Verlag, Stuttgart
Klinke, Pappe, Silbernagl. Physiologie, 5. Auflage 2005
Blood flow in the renal medulla

The hyperosmolarity and the medullar gratient would be washed out quickly, if the blod flow and the form of blood wessels would be conventional. The loop form structure of Vasa Recta prevents the dilution of renal medulla. Countercurrent system does not allow the quickly transport of NaCl and urea.
Clearance-principle

Clearance is the amount of plasma that is cleared of a substance during one minute (or one sec).

It is a virtual plasma volume characteristic to a substance in question.

\[ C = \frac{U \times V}{P} \]

Osmotic clearance: \[ C_{osm} = \frac{U_{osm} \times V}{P_{osm}} \]

Free water clearance: \[ C_{H2O} = V - C_{osm} \]

\[ C_{H2O} = V(1 - \frac{U_{osm}}{P_{osm}}) \]
The concentration of urin will be inhibited through:

- Karboanhydrase inhibitor (Acetazolamide)
- Loop diuretics (Inhibition of Na⁺, K⁺, 2Cl⁻-symporters)
- Thiazide (Inhibition of Na⁺/Cl⁻ cotransporter)
- ATII receptor antagonists (Losartan)
- Aldosteron antagonists (Spironolakton)
- Potassium deficit (inhibits the Na⁺, K⁺, 2Cl⁻-symporter)
- Hyperkalcaemia (Decreasing the permeability of tight junctions, Ca²⁺-receptors inhibiting the Na⁺, K⁺, 2Cl⁻-symporter)
- Proteipoor nutrition
- Renal inflammation (Dilatation of Vasa recta)
- Increase of blood pressure
- Osmotic diuresis (filtration of no or partial resorbable osmotic active substances)
- Diabetes insipidus (renal, central)
Volume regulation (Na\(^+\) household)

**Na\(^+\) intake**
- Na\(^+\) content of drinks and food between 10 and 600 mmol
- Na\(^+\) (100-400 mmol/day in general).
- No physiological mechanism of Na\(^+\) intake

**Na\(^+\) loss**
- Sweat
- Stool
- Urine (100-400 mmol/day).

**Regulation of salt household**
- Through salt loss.

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**Tubular Transport**

About 99% of filtrated water and more than 90% of the filtrated substances will be resorbed. Additionally some substances will be secreted.
Mechanisms of Na\(^+\)-resorption in the whole nephron

- Na/H antiporter
- Na/S symporter
- Paracellular transport
  
  Proximal Tubule  
  (acetazolamide inhibits)

- Na/K/2Cl symporter
- Paracellular transport
  
  Loop of Henle  
  (furosemide inhibits)

- Na/Cl Sympporter
- Na channels
  
  Distal Nephron (thiazide inhibits)  
  ATII rezeptor and aldosteron antagonists

Effector mechanisms

1. GFR

2. Renin-Angiotensin-Aldosterone system
   Adrenal cortex glomerular zone (mineralocorticoid)
   Na\(^+\) and K\(^+\) ion exchange in the distal tubule and collecting duct

3. “third factor”
Renin-angiotensin-aldosteron system

A juxtaglomerular apparatus
myoepithel cells of vas afferents,
macula densa in distal tubulus,
mesangial connective tissue,

*Renin* (66500 d)

*angiotensinogen* (alfa2-globulin, liver),

*Angiotensine I* (10 amino acid (ACE, angiotensine converting enzyme)

*Angiotensine II* (8 amino acid)

*Angiotensine III*
Renin secretion increased by

1. decreased renal blood flow
2. amount and chemical composition of tubular fluid at macula densa,
3. stimulation of renal sympathetic nerve,
4. extracellular hypovolemia (bleeding)
Renin secretion decreased by:

1. prostaglandines (PGE$_2$, PGD$_2$, PGI$_2$)
2. atrial natriuretic factor (ANF)
Angiotensine II effects

1/ Blood pressure
   vasoconstrictor (systolic and diastolic pressures increase)

2/ Aldosterone

3/ Central effects (hypothalamus)
Factors increasing aldosterone secretion:

angiotensine II
decreased atrial natriuretic factor,
increased plasma K^+,
ACTH,

Regulation of Aldosterone secretion
Principal (main) cell (controlled Na\(^+\) resorption)

Aldosterone dependent resorption
In late distal tubulus and in the collecting duct can be found these cells.
Luminal Na\(^+\) und K\(^+\)- channels
The cells resorbe Na\(^+\) and secrete K\(^+\)
Increased Na\(^+\)-Resorption
Increased K\(^+\)-Sekretion und K\(^+\)-Excretion

Principal cell

Intercalated cell Typ A

Intercalated cell Typ B
Atrial natriuretic factor (ANF)

Right atrium

28 (21 - 73) amino acid (2800-13,000 dalton).

126 amino acid precursor (pro-ANF (atriopeptinogen)).

ANF secreted

Increased atrial stretch (hypervolemia)

ADH

Effects of ANF

1. Vasodilatation
2. increased GFR
   (dilation of the afferent arteriole)
3. inhibition of renin secretion
4. decreased in aldosterone secretion
5. inhibition of ADH
6. natriuresis and water diuresis
7. decreased cardiac output