Normal values connected to these topics

- urine osmotic concentration: 70-1200 mosmol/L
- urine specific gravity: 1001-1038 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 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
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.

---

Tubular Transport

About 99% of filtrated water and more than 90% of the filtrated substances will be resorbed. Additionally some substances will be secreted.

<table>
<thead>
<tr>
<th>Proximal convoluted tubule</th>
<th>Loop of Henle</th>
<th>Distal convoluted tubule and collecting duct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of filtered sodium reabsorbed</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>Percent of filtered water reabsorbed</td>
<td>70</td>
<td>10</td>
</tr>
</tbody>
</table>
Na⁺ transport in the proximal tubule

Abb. 35–11. Transportprozesse im proximalen Tubulus. CA = Carboanhydrase (es existiert sowohl ein intrazelluläres als auch ein extrazelluläres Enzym), S = Substrat (es existieren eine ganze Reihe von Symporten mit Na⁺, z. B. mit Glukose, Galaktose, verschiedenen Aminosäuren, Laktat, Phosphat, Sulfat), A⁻ = Anionen (Cl⁻, HCO₃⁻) und organische Säureionen. Transportprozesse für organische Kationen sind nicht eingezeichnet.
Loop of Henle - thin, descending segment
Weak permeability to solutes, Sodium secretion!!!
Passive transport

Loop of Henle - thin, ascending segment
1. Not permeable to water !!!
2. Freely permeable to Na⁺ (and Cl⁻)
3. Passive Na⁺ transport
Loop of Henle - thick, ascending segment
1. No water permeability !!!
2. Active Na\(^+\) and Cl\(^-\) reabsorption
3. Passive Na\(^+\) reabsorption, paracellular
Distal nephron – distal convoluted

Secondary active Na\(^+\) resorption

No paracellular Na\(^+\) resorption
Until this point there were NO controlled Na\textsuperscript{+} transports !!!

Mechanisms of Na\textsuperscript{+}-resorption in the whole nephron

- **Na/H antiporter**
  - Proximal Tubule
  - (acetazolamide inhibits)

- **Na/S symporter**
  - Paracellular transport

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

- **Na/Cl Symporter**
  - Distal Nephron (thiazide inhibits)

**Na channels**
- (Aldosteron dependent)

**AT2 receptor and aldosteron antagonists inhibit**
**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-aldosterone 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*
JUXTAGLOMERULAR APPARATUS

Control of renin secretion
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/ **Aldosteron**

3/ **Central effects (hypothalamus)**
Regulation of Aldosterone secretion

Factors increasing aldosterone secretion:

angiotensine II

decreased atrial natriuretic factor,

increased plasma K⁺,

ACTH,
**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

---

**Na\(^+\)- transport in the principal cells (controlled reabsorption, Aldosterone!)**
Other effector organs of aldosterone

- The effects are the same as on the principal cells of the collecting duct
- Salivary glands
- Sweat glands
- Small intestine
- Large intestine

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  
   (dilatation 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

---

**Water household**

**Water intake**  
2100-3400 ml/day  
Fluid intake  
1000-2000 ml/day  
Water content of foodstuffs  
800-1000 ml/day  
Oxidative water  
300-400 ml/day

**Water output**  
2100-3400 ml/day  
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)**
Control of loss of water

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-Ca^{2+} 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*
### ADH secretion

<table>
<thead>
<tr>
<th>Increased by</th>
<th>Inhibited by</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. High osmolarity of the blood</td>
<td>1. low osmolarity</td>
</tr>
<tr>
<td>2. Hypovolemia</td>
<td>2. Hypervolemia</td>
</tr>
<tr>
<td>(inhibits ANP secretion)</td>
<td></td>
</tr>
<tr>
<td>3. Standing</td>
<td>3. Lying in horizontal position</td>
</tr>
<tr>
<td>↓ ANP</td>
<td>↑ ANP</td>
</tr>
<tr>
<td>4. venous stasis</td>
<td>4. Alcohol</td>
</tr>
<tr>
<td>5. pain, exercise</td>
<td></td>
</tr>
</tbody>
</table>

### The osmolarity of the tubular fluid

![Diagram showing the osmolarity of the tubular fluid](image-url)
The concentration and dilution of the urin

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 (PGE$_2$, PGD$_2$)
Concentration and Dilution of Urine

Countercurrent multiplication

Medullary gradient

300 mosm/kg-1200 mosm/kg

Horizontal 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

2020.03.03.
Blood flow in the renal medulla

The hyperosmolarity and the medullar gradient would be washed out quickly, if the blood flow and the form of blood vessels 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 rezeptor antagonists (Losartan)
- Aldosteron antagonistsen (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 (Vasodilatation)
- Increase of blood pressure
- Osmotic diuresis (filtration of no or partial resorbable osmotic active substances)
- Diabetes insipidus (renal, central)

Potassium household (Learning objective: 80)

Factors determining K⁺ content of the body

1. K⁺ intake and output,
2. distribution of potassium between the intracellular and extracellular space.

<table>
<thead>
<tr>
<th>INTAKE</th>
<th>OUTPUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drinks, food</td>
<td>50-100 mmol/day</td>
</tr>
<tr>
<td>Urine</td>
<td>45-90 mmol/day</td>
</tr>
</tbody>
</table>

Sum          50-100 mmol/day  50-100 mmol/day
Distribution of K\(^+\) between the intracellular and extracellular fluids

\[ \text{extracellular: } 80 \text{ mmol} = (4 \text{ mmol/l}) \times 20 \]  
\[ \text{intracellular: } 6000 \text{ mmol} = (150 \text{ mmol/l}) \times 40 \]

\[ K^+ \]

- **K\(^+\) reabsorption**
  - proximal nephron 1. and 2. segments
  - thick segment

- **K\(^+\) secretion**
  - proximal tubule 3. segment
  - thin descending limb
  - distal tubule

*regulation: aldosterone, (insulin)*
Potassium transport in the loop of Henle
Potassium transport in the distal tubule cell

Potassium transport in the principal and intercalated cells

Principal cell (aldosteron effect)

Intercalated cell Typ A

Intercalated cell Typ B
Dependence of resting membrane potential of myocardiac cells from extracellular K⁺ concentration

Hormonal regulation of extracellular K⁺ concentration

- Aldosterone
- Insulin: - direct stimulation of Na⁺-K⁺ pump
  - Stimulation of Na⁺-H⁺ antiporter in liver muscle and fett tissue
- Katecholamines direct stimulation of Na⁺-K⁺ pump
Isohydria and K+ Homeostasis are coupled

Hyperkalemic acidosis
Hypokalemic alcalosis