DISTURBANCES OF WATER & ELECTROLYTE METABOLISM
PART 1 – WATER & SODIUM

LECTURE FROM PATHOPHYSIOLOGY
school year 2009/2010
OLIVER RÁČZ
INSTITUTE OF PATHOPHYSIOLOGY,
MEDICAL SCHOOL, UPJŠ KOŠICE

<table>
<thead>
<tr>
<th>Ion</th>
<th>Amount in body</th>
<th>Plasma mmol/l</th>
<th>Cells mmol/l</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium, Na⁺</td>
<td>92 g 4 mol</td>
<td>141</td>
<td>10</td>
</tr>
<tr>
<td>Potassium, K⁺</td>
<td>100-140 g 2,5-3,5 mol</td>
<td>4</td>
<td>155</td>
</tr>
<tr>
<td>Calcium, Ca²⁺</td>
<td>1200 g 30 mol</td>
<td>2,5</td>
<td>&lt; 0,001 (uneven)</td>
</tr>
<tr>
<td>Magnesium, Mg²⁺</td>
<td>26,5 g 1,1 mol</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>Chloride, Cl⁻</td>
<td>50 g 1,4 mol</td>
<td>103</td>
<td>8</td>
</tr>
<tr>
<td>Phosphate (as phosphorus)</td>
<td>775 g 25 mol</td>
<td>1</td>
<td>65</td>
</tr>
</tbody>
</table>
Sodium – kitchen salt in our diet

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volume, litres</th>
<th>% of body mass</th>
<th>% of total water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Europe</td>
<td>10 – 12 g/d</td>
<td>230 – 276 mmol/d</td>
<td></td>
</tr>
<tr>
<td>Recommended</td>
<td>2 – 7</td>
<td>46 – 161</td>
<td></td>
</tr>
<tr>
<td>Hypertonics</td>
<td>&lt; 3,5</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Strict vegetarians</td>
<td>0,75</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

Ca & Mg deficiency is frequent!

Ca: 800 mg/d = 20 mmol/d
the same for children and young gravidity & lactation – 1200 mg/d!

Mg: 300 – 350 mg/d = 12-14 mmol/d
more in puberty, gravidity, lactation & physical exercise
USA: 143 – 266 mg/d

DISTRIBUTION OF WATER IN HUMAN BODY

<table>
<thead>
<tr>
<th>Compartment</th>
<th>Volume, litres</th>
<th>% of body mass</th>
<th>% of total water</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICS*</td>
<td>28</td>
<td>40</td>
<td>67</td>
</tr>
<tr>
<td>ECS</td>
<td>14</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>ISF</td>
<td>11</td>
<td>15,7</td>
<td>26</td>
</tr>
<tr>
<td>IVF</td>
<td>3</td>
<td>4,3</td>
<td>7</td>
</tr>
<tr>
<td>SUMMA</td>
<td>42</td>
<td>60</td>
<td>100</td>
</tr>
</tbody>
</table>

Third space! small virtual volume, dynamic exchange – important in pathological conditions

*10^{14} cells
AGE DEPENDENCE OF FLUID HOMEOSTASIS

<table>
<thead>
<tr>
<th>AGE</th>
<th>TOTAL WATER, %</th>
<th>DAILY EXCHANGE, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>newborn &amp;</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>3-6 mo.</td>
<td>70</td>
<td>14-16</td>
</tr>
<tr>
<td>7-12 mo.</td>
<td>60</td>
<td>12-15</td>
</tr>
<tr>
<td>adult man</td>
<td>60</td>
<td>2-4</td>
</tr>
<tr>
<td>adult woman</td>
<td>51</td>
<td>2-4</td>
</tr>
</tbody>
</table>

& ECS > ICS, danger of dehydration
In old age further ↓ & impaired adaptation, danger of dehydration

BALANCE & DYNAMICS

intake = output
+ 1,2 – 1,5 beverage
+ 1,0 food
+ 0,3 – 0,5 metabolism
- 1,0 – 2,0 urine
- 0,6 – 0,8 perspiration
- 0,4 – 0,5 respiration
- 0,1 stool
2,5 – 3,0 liters/day

- KIDNEYS = 180 l/d
- GIT = 8,2 l/d
  - saliva 1,5
  - stomach 2,5
  - pancreas 0,7
  - bile 0,5
  - guts 3,0

- THIRD SPACE
**OSMOLALITY & OSMOTIC GAP**

Volume change (water loss)

Changes in concentration of solutes without change of the amount!

Compensatory mechanisms: retention or excretion of ions, adjustment of concentrations

Osmolality = 2*[^Na] + [glucose] + [urea]

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volume 5 l

♣ = 25 5.0/l
♠ = 25 5.0/l
✽ = 3 0.6/l
∑ = 53 10.6/l

---

volume 4 l

♣ = 25 6.25/l
♠ = 25 6.25/l
✽ = 3 0.75/l
∑ = 53 13.25/l
Loss of isotonic fluid

Reduction of ECS, thirst
no change of ICS
normal plasma sodium

Loss of hypotonic fluid

Reduction of ECS.
Hypernatremia compensated through water shift from ICS
Shrinkage of cells
Salt loss

Hyponatremia compensated through water shift from ECS into ICS,
Reduction of ECS, swelling (oedema) of cells

DISTURBANCES OF THE SYSTEM

- No pure forms – loss of water, salt...
- Immediate reaction of compensatory systems
- ECS is in contact both with external environment and with ICS
- ICS is in contact only with ECS
- Plasmatic concentrations are not amounts and does not inform on dynamics of compounds
POSSIBLE CAUSES AND MECHANISMS

- Extreme deviations of external environment
  Dehydratation from insufficient water intake
- Disturbances caused by damaged function of effector systems (kidneys, GIT, etc.)
  Diarrhoea, vomitus, kidney diseases
- Disturbances caused by erroneous regulation (CNS, ADH, aldosterone)
  Diabetes insipidus, Conn sy., SIADH
  Heart failure & RAA activation

DECREASED WATER INTAKE

- 1 – 2 days: hyperosmotic hypovolemia
  thirst, compensated through ADH/RAA
- Pespiratio insensibilis 5 ml/hour
  ↑ fever and in hot environment
- In old people and kidney diseases the concentrating capacity of kidneys is decreased
- Later: exsicosis, dehydration, > 20 % death
WATER DEFICIENCY – REDUCTION OF ECS

Causes
- Insufficient fluid intake
- Inability to drink (loss of consciousness)
- Losses through GIT (diarrhoe, vomitus)
- Losses through kidneys (diuretics, osmotic diuresis, kidney diseases, m. Addison)
- Losses through skin (increased sweating, burns)
- Displacement into third place (ileus, ascites)
- Blood loss (?)

Symptoms: hypotension, tachycardia, dry skin, thirst, oliguria & decreased sodium excretion, increase of hematocrit

WATER RETENTION – ECS EXPANSION

Causes
- Increased fluid intake
- Increased intake & disturbed regulation – SIADH
- Kidney failure
- Nephrotic sy.
- Heart failure
- Liver cirrhosis

Symptoms: Oedema.
Hypernatraemia
>150 / 160 mmol/l

Low osmolality of urine – diabetes insipidus
Osmolality of urine ≅ plasma – osmotic diuresis
(diabetes mellitus)
Osmolality of urine > plasma – dehydratation
  diarrhoea, vomitus sweating
Conn syndrome (hyperaldosteronism)
  → hypernatremia, hypokalemia

Hyponatraemia
<130 / 120 mmol/l

Plasma osmolality high → hyperglycemia ?!
Plasma osmolality low →
  Na in urine > 20 mmol/l & hypovolemia
    m. Addison, diuretics
    salt losing nephritis
  Na in urine < 20 mmol/l & hypovolemia
    diarrhoea, vomitus, sweating with
    inadequate fluid replacement
  Na in urine < 20 mmol/l & oedema
    heart failure, cirrhosis, nephrotic sy.
    SIADH
DISTURBANCES OF ADH SECRETION
AND EFFECTS – I.

Diabetes insipidus, neurogenic (AD)
  AVP gene mutation
Acquired forms – damage of hypothalamus
  Complete & partial forms
Diabetes insipidus, renal (X-related & AR)
  Receptor (X) or water channel protein (AR)
  gene mutations
Acquired – kidney diseases

DISTURBANCES OF ADH SECRETION
AND EFFECTS – II.

SIADH – inadequate secretion of ADH (lack of suspension)
  Expansion of ECS
hyponatremia, hypoosmolality
High urine osmolality & high Na in urine
Increased ANP
Renal & endocrine functions intact

Hereditary forms and stress ??!!
DISTURBANCES OF WATER & ELECTROLYTE METABOLISM
PART 2 – POTASSIUM

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POTASSIUM HOMEOSTASIS

- Serum concentration: 3.8 – 5.5 mmol/l*
- Total amount depends on muscle mass
  (young > old; man > women)
  37 – 52 mmol/kg body mass
- Intake: 2-6 g/d = 50-150 mmol/d
- Excretion through kidneys 10 – 20 mmol/d
  (0.4 – 0.8 g/d).
- Inverse association with Na excretion
- GIT excretion is important in kidney failure and in pathological conditions (diarrhoea)

*Depends on method. Preanalytic errors - hemolysis!
FUNCTIONS OF POTASSIUM & INTERPRETATION OF RESULTS

Functions
- intracellular osmotic pressure
- resting & action potential
- enzyme activity, proteosynthesis

Problems:
1. assessment of cell homeostasis from extracellular concentration
2. pH changes: exchange H/K between ECF/ICF

INTERNAL & EXTERNAL BALANCE

internal – ECF/ICF
- acidosis: H⁺ enters the cells, K⁺ out into ECF
- alkalosis: H⁺ into ECF, K⁺ enters the cells
- K⁺ entry into cells: insulin (together with glucose), aldosterone, adrenaline
- rapid cellular proliferation (treatment of pernicious anaemia with B₁₂ vitamin
- cell necrosis, hemolysis (crush sy, malignancies), K⁺ into ECF

external – ECF/environment
- kidney or GIT retention/losses, parenteral intake
- dietary deficiency/excess as an additional factor
HYPOKALAEMIA - SYMPTOMS

- hypokalaemia < 4.0 mmol/l
- significant < 3.5 mmol/l
- dangerous < 3.0 mmol/l

- Membrane hyperpolarisation
- Weakness, constipation, ileus, hypotonia
- Depression, confusion
- Arrhythmia, potentiation of digitalis toxicity
- ADH resistance, polyuria, polydipsia
- ECG flat/inversed T, prolonged PR, ST depression, prominent U

HYPOKALAEMIA - CAUSES

Disorders of external balance
- GIT – diarrhoea, vomitus, tumors of colon, rectum, pancreas
- Kidneys - diuretics, polyuric stage of renal failure, hereditary tubulopathies,
- Primary & secondary hyperaldosteronism, abuse of liquorice, Cushing, ectopic ACTH production

Glycyrrhiza glabra. Glycyrrhizin, a sweet substance
Weak corticominetic & fitoestrogen effect
Component of herb teas, nonalcoholic drinks and beer
HYPOKALAEMIA - CAUSES

Disorders of internal balance
- Treatment of diabetic hyperglycaemia with insulin
  (K+ entry into cells together with glucose)
- Alkalosis
- Rapid cellular proliferation
- Familial hypokalaemic periodic paralysis (hereditary)

HYPERKALAEMIA - SYMPTOMS
- hyperkalaemia < 5.5 mmol/l
- significant < 6.5 mmol/l
- dangerous < 7.5 mmol/l
- Low resting potential, short cardiac action potential,
  increased speed of repolarization
- Can kill without warning
- Ventricular fibrillation and cardiac arrest may be the first
  signs! (if you do not check K & ECG)
- ECG: abnormal/absent P; broad QRS,
  peaked T, ST depression
HYPERKALAEMIA - CAUSES

Disorders of external balance

- Decreased excretion. Under GFR 15 ml/min always. 
  Anuria: K increase 1 mmol/l daily
  In mild impairment of kidney function only when other factors are present
- Increased intake (infusions, NaCl substitution) only in the case of impaired kidney function
- m. Addison, adrenogenital sy., inhibitors of angiotensin converting enzyme

Disorders of internal balance

- Acidosis
- Cell necrosis - rhabdomyolysis, burns, cytostatic treatment of malignanacies
- Digitalís overdose
- Hyperkalaemic periodic paralysis (hereditary)
- Malignant hypertermia (hereditary)
DISTURBANCES OF WATER & ELECTROLYTE METABOLISM
PART 3 – CALCIUM & MAGNESIUM

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CALCIUM

- Total body 1200 g 30 mol
- ECF 0,9 g 22,5 mmol
- Plasma 0,36 g 9,0 mmol
- Bone / ECF exchange 500 mmol/d
- Daily losses 25 mmol/d (1g)
  - urine 6 mmol (240 GF – 234 reabsorption)
  - faeces 19 mmol (+25 food, 12 in, + 6 secr.)
  - skin 0,3 mmol

Small changes in fluxes can have profound effect of plasma Ca
FUNCTIONS OF CALCIUM

- Structural
- Neuromuscular
- Bone, teeth
- Control of excitability; Neurotransmitter release
- Muscle contraction
- Coagulation (§ 22)
- Messenger

Blood
- Control of excitability; Neurotransmitter release
- Muscle contraction
- Coagulation (§ 22)
- Messenger

Signal systems
- Control of excitability; Neurotransmitter release
- Muscle contraction
- Coagulation (§ 22)
- Messenger

PLASMA CALCIUM

TOTAL
2,25 – 2,60 mmol/l

diffusible 54 %
protein-bound 46 %
free - ionized 47 %
complexed 7 %

CLINICAL CHEMISTRY: TOTAL OR IONIZED?
EC CALCIUM REGULATING HORMONES

**PTH & calcitriol!** Calcitonin is of minor importance. Also regulation of phosphorus and perhaps magnesium

- **PTH** – a 84 AA peptide from 115 AA precursor. AAs 1-34 are active
- Short half life
  - Calcitriol is a steroid hormone derived from vit. D
  - The 2nd hydroxylation in liver is strictly controlled
  - Calbindin D in gut
  - Receptors in other tissues – role in cellular proliferation and differentiation and in immune response?

FUNCTIONS OF PTH

**BONE**
- Release of calcium \( \uparrow [\text{Ca}^{2+}] \)
- Osteoclastic resorption

**KIDNEY**
- Calcium reabsorbtion \( \uparrow [\text{Ca}^{2+}] \)
- 2nd hydroxylation of vit.D \( \uparrow \) Ca, P absorbtion
- Phosphaturia \( \downarrow [\text{PO}_4^2-] \)
- Decrease of \( \text{HCO}_3^- \) reabsorbtion \( \downarrow \) pH
HYPOCALCAEMIA - CAUSES

- Hypoparathyroidism
  - Congenital (with Di George sy.)
  - Acquired – autoimmune, surgery, hemochromatosis, tumors
- Pseudohypoparathyroidism
  - 2 hereditary disorders of PTH signaling pathway (cAMP dependent)
- Magnesium deficiency (pseudo ?)
- Deficiency of vitamin D (!)
- Disorders of vitamin D metabolism – end stage renal disease
- Acute pancreatitis, transfusions with citrate, neonatal

HYPOCALCAEMIA - SYMPTOMS

- Stupor, numbness, paraesthesia
- Muscle cramps and spasms „tetany“
- Laryngeal stridor
- Convulsions
- Chvostek+ Trousseau+, long QT on ECG
- Cataract in chronic hypocalcaemia
- Rickets (rachitis) in vitamin D deficiency

OSTEOPOROSIS ???
HYPERCALCAEMIA - CAUSES

- COMMON (90% of all)
  - Primary hyperparathyroidism
  - Malignancies – bone metastasis (?), PTHrP and other humoral factors
- LESS COMMON
  - Thyreotoxicosis, sarcoidosis
- UNCOMMON
  - Lithium treatment, tbc, immobilisation, adrenal failure, renal failure, hereditary
- BUT ALSO HYPERPARATHYROIDISM WITHOUT HYPERCALCAEMIA
  - Compensatory in vitamin D deficiency, renal disease

HYPERCALCAEMIA - SYMPTOMS

- Weakness, tiredness, weight loss
- Impaired concentration, drowsiness (coma)
- Anorexia, nausea, vomiting, constipation
- Polyuria, dehydration
- Renal calculi, nephrocalcinosis
- Short QT, arrhythmias
MAGNESIUM

- 60% in bones, higher in ICF than in ECF
- Only 0.3% in blood, 30% protein bound
- Serum 0.7 – 1.0 mmol/l
- Regulator is not known! adrenal medulla, insulin, parathormon ???
- Regulated resorption from GIT?
- 8 mmol/d is enough? Is deficiency common?
- Excretion through urine and stool

Neuromuscular excitability (inhibition – mediated through decreased secretion of acetylcholine?)

- Bone structure
- Enzyme activity, energy production, transport mechanisms, ribosomes
- Regulation of haemocoagulation and membrane function
MAGNESIUM

- Cardioprotective antiischemic, antihypoxic effects
- Sedative effect on NS
- Antihypertensive
- Antithrombotic

Deficiency associated with soil and plant deficit ꞏ grass tetany of cattle
- Some drugs and stress can increase excretion
- Unhealthy diet (alcohol)
- High doses of calcium (!)

CONSEQUENCES
- Spasmophilia is more often a consequence of Mg deficiency as of Ca
- Tiredness, irritability, tremor
- Dysmenorea, preeklampsia
- arrythmias