MUNI
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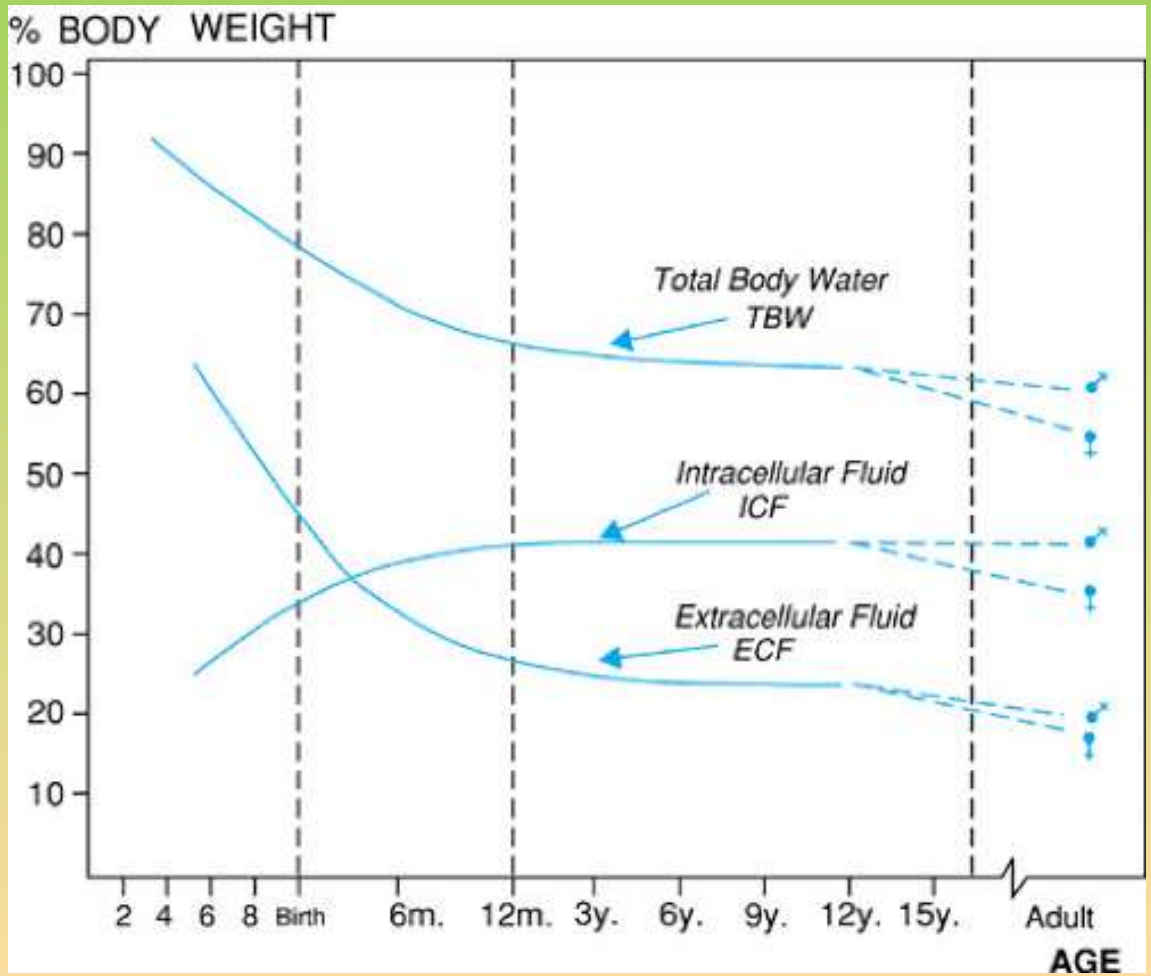
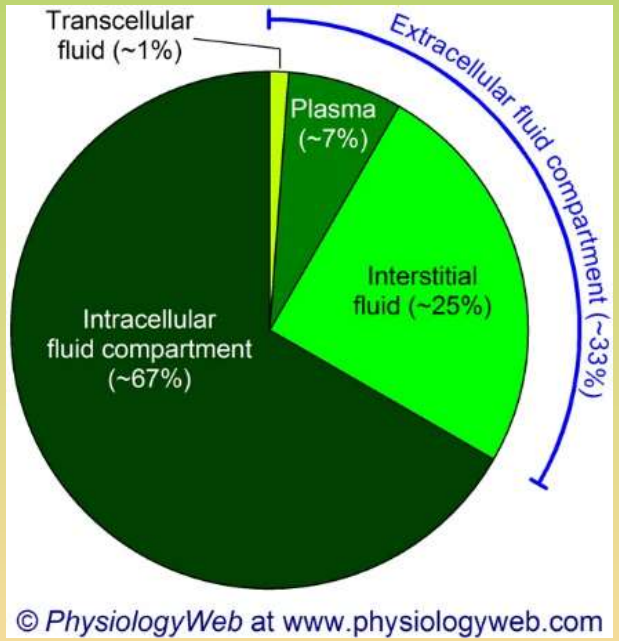
Disorders of osmolarity and ionic balance

Total body water – age and sex



Compartments of body water

- Intracellular fluid (ICF, approx. 2/3)



- Extracellular fluid (ECF – approx. 1/3)
  - Plasma
  - Interstitium
    - Lymph has a composition corresponding to interstitial fluid
  - Transcelullar fluid (CSF, eye fluid, effusions in pathological conditions)
    - Primary urine actually acts as transcellular fluid as well

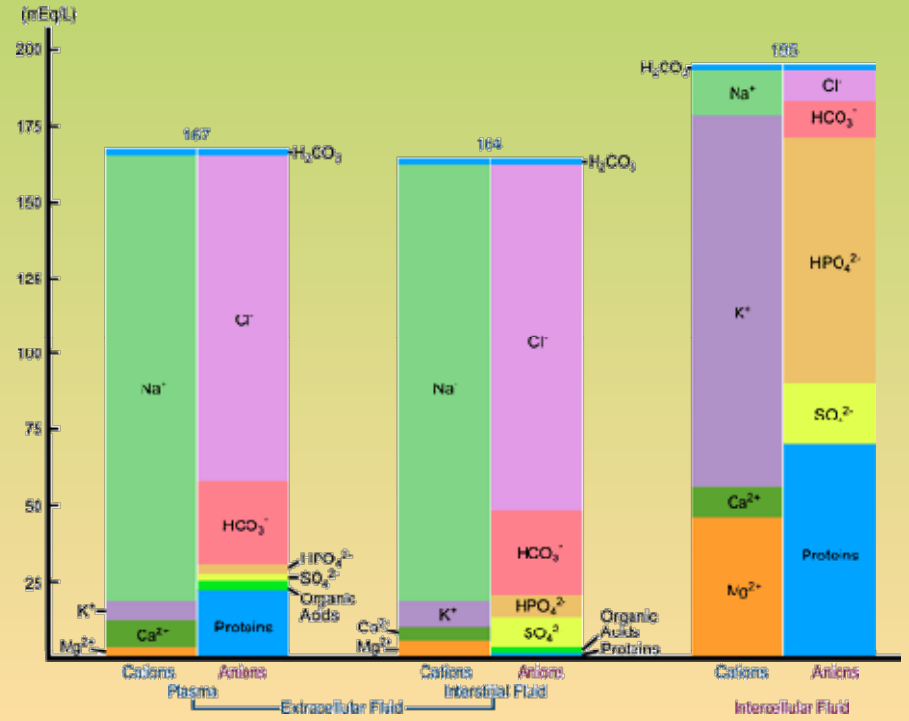
Composition of ICF and ECF

ICF: more proteins, K^+, Mg^{2+}, fosfáty ($H_2PO_4^-$/HPO_4^{2-}); Ca^{2+} is located in specialized compartments

ECT: Na^+, Ca^{2+}, Cl^-, HCO_3^- (alkalic environment)

plasma contains more proteins compared to interstitial and transcelullar fluid

Same osmolarity (285-295 mosmol/l – a portion of proteins + phosphates in ICF is insoluble, as well as Mg^{2+} on the cationic side; in the ECF this concerns only a little amount of Ca^{2+} and proteins)

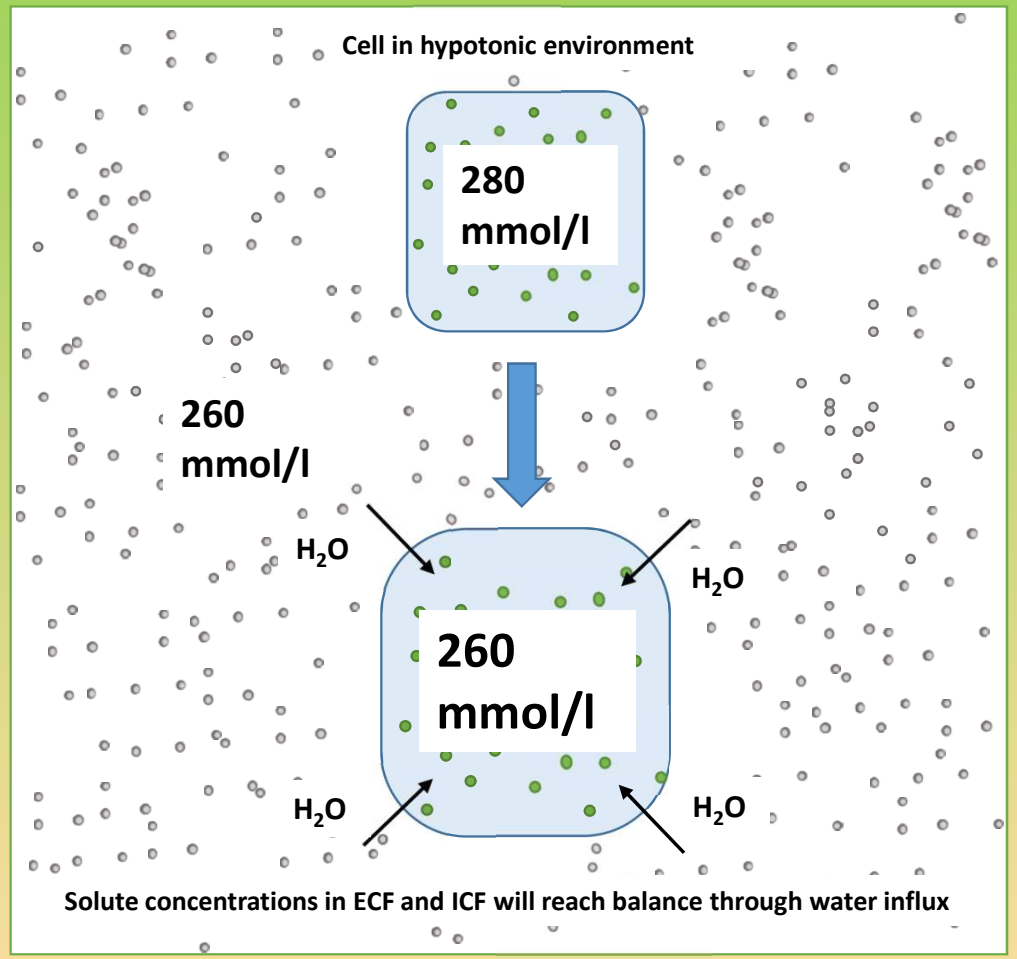


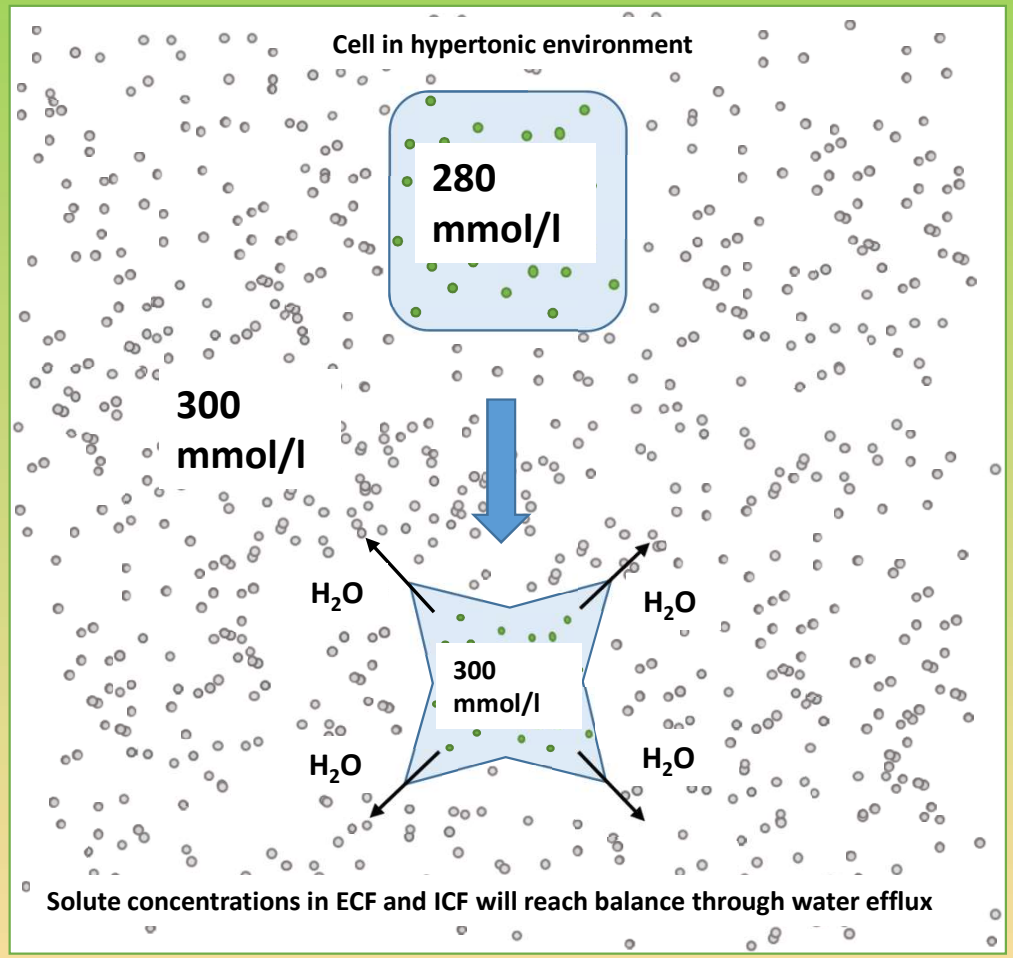
Parameter	ECF	Plasma	CSF
Na^+ (mEq/l)	136-145	150	147
K^+ (mEq/l)	3.5-5	4.6	**2.9 (0.62)**
Ca^{2+} (mEq/l)	3.4	4.7	**2.3 (0.49)**
Mg^{2+} (mEq/l)	1.50-2.5	1.6	**2.2 (1.39)**
Cl^- (mEq/l)	**110-118**	105.0	**120 (1.14)**
HCO_3^- (mEq/l)	22-28	24.8	25.1
pH	7.35-7.45	7.38-7.42 A-WB	7.4
P_{O2} (mmHg)	**35**	75-100 A-WB	**42**
P_{CO2} (mmHg)	39.5	35-45 A-WB	**50.2**
Glucose (mg/ml)	70-110	70-110	**64**
Osmolality (mOsm kg^{-1} H_2O)	280-296	280-296	289
Temperature (°C)	36.6-37.3	37.0	**37.7**

A-WB: Arterial whole blood; ECF (extracellular fluid) and CSF (cerebrospinal fluid) values different from plasma are indicated in bold font.

- Agnati et al., 2017

Osmosis – water transfer in changing osmolarity





Extracellular solutes

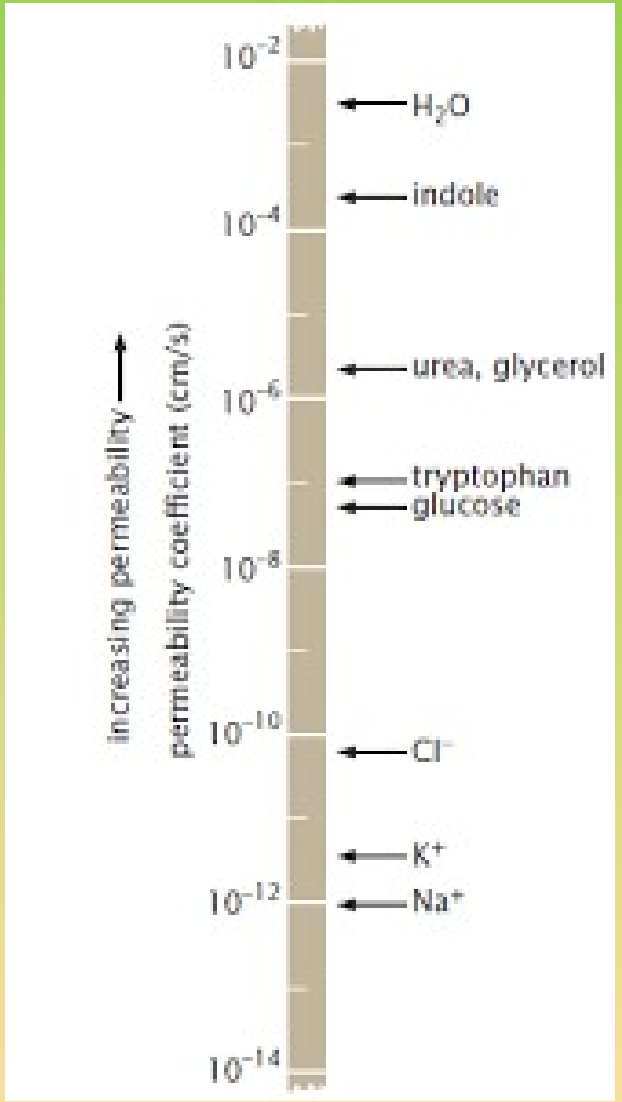
Intracellular solutes

Osmolarity and osmolality

- Osmolarity – concentration of osmotically active particles (per a unit of volume)
  - 1 mol of NaCl disociates into na 1 mol of Na^+ and 1 mol of Cl^- and has thus the same osmolarity as 2 mols of glucose
- Osmolality – similar, but calculated per a unit af mass
  - In practice, both values are similar in highly diluted water solutions
- Osmotic pressure – $\pi = R.T.\Sigma(c.i)$
- Estimation of overall body osmolarity based on plasma solutes: $2Na^+ + 2\ K^+$ + urea + glucose
  - i.e. double of plasma cations + neutral substances
  - the principle of elecroneutrality : Cl^- a and other anions are evened up by HCO_3^- and vice versa, which has consequences for ABB, but not for osmolarity
  - natremia is therefore the main factor of plasma osmolarity

Tonicity (effective osmolarity)

- Osmolarity of solutes, which don't pass through a membrane and generate thus osmotic pressure (i.e. they are osmotically active)
- Substances that passes membranes:
  - Blood gases – non-polar
  - Ethanol
  - Urea – polar, but has many channels (like water)
    - artificial phospholipid bilayer: σ=0,95
    - most membranes and capillary wall: σ<0,1
    - hematoencephalic barrier: σ=0,5 (danger in rapid correction of uremia → cerebral oedema)
- Cells contain many osmotically active anions and they must expend energy for $3Na^+/2K^+$ ATP-ase, which maintains the same tonicity at both sides of the membrane

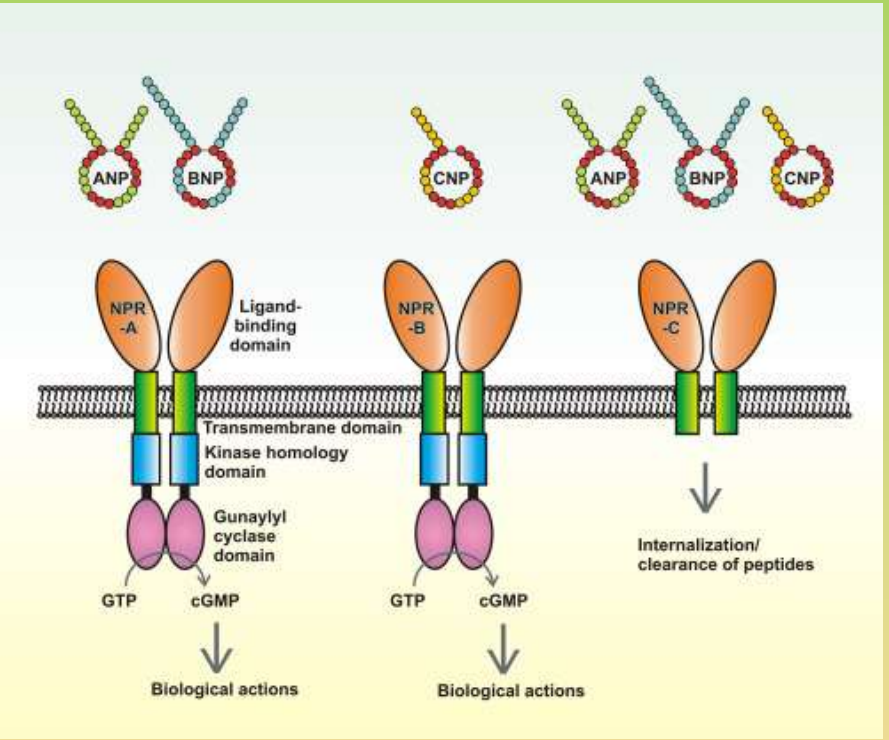


Regulation of osmolarity and circulating volume

- RAAS (esp. angiotensin II/III and aldosterone) – increases circulating volume and maintains osmolarity (↑ Na^+ and water), + vasoconstriction
- ADH (V2 receptors) – decreases osmolarity by pure water reabsorption in kidney collecting ducts (↑ water), + vasoconstriction (high levels - shock)
- Natriuretic peptides – decrease circulating volume (↓ Na^+ and water), + vasodilation

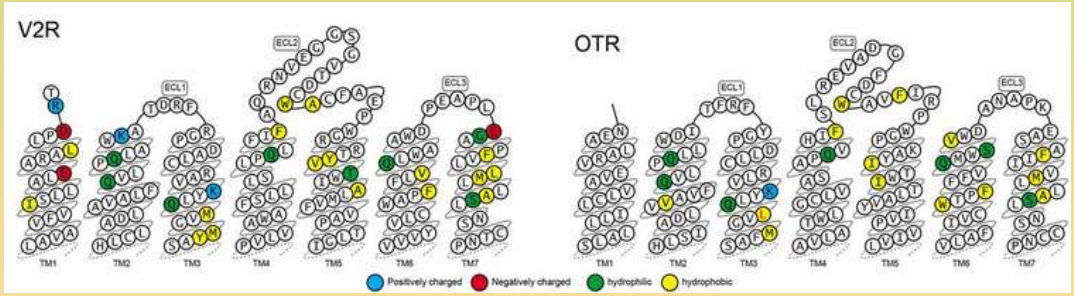
Natriuretic peptides

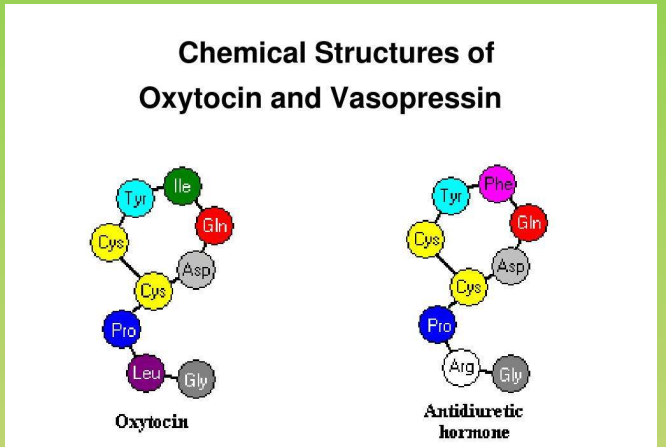
- ANP – stored in granules of atrial cardiomyocytes – „rapid reaction substance“ in ↑ venous return
- BNP – mainly ventricular cardiomyocytes (and brain), no storage, long elimination halftime – chronic heart failure (marker)
- CNP – vascular endothelium – only vasodilation, no natriuretic effects
- Urodilatin – alternative (longer) transcript of the ANP gene, paracrine action in the kidneys

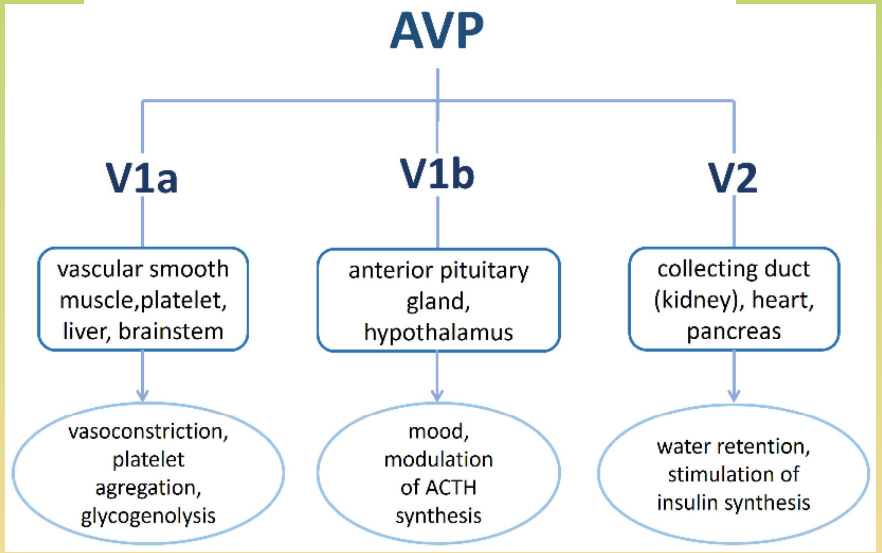


Antidiuretic hormone

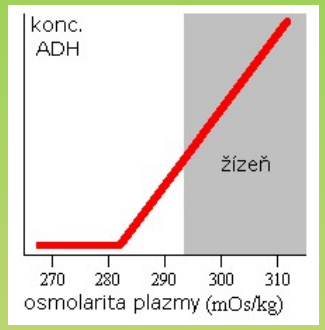
- Produced in nucleus supraopticus (SON) and nucleus paraventricularis (PVN) together with oxytocin, released from posterior pituitary (both hormones also act as neurotransmitters linked to social behaviour)
- Hypothalamic ”osmostat” and ADH
  - reacts to 1% deviation from baseline
  - ADH production is supressed by
    - lowering of osmolarity, alcohol, cold environment
- Osmotic and volume balance is regulated mostly using the V2 receptors

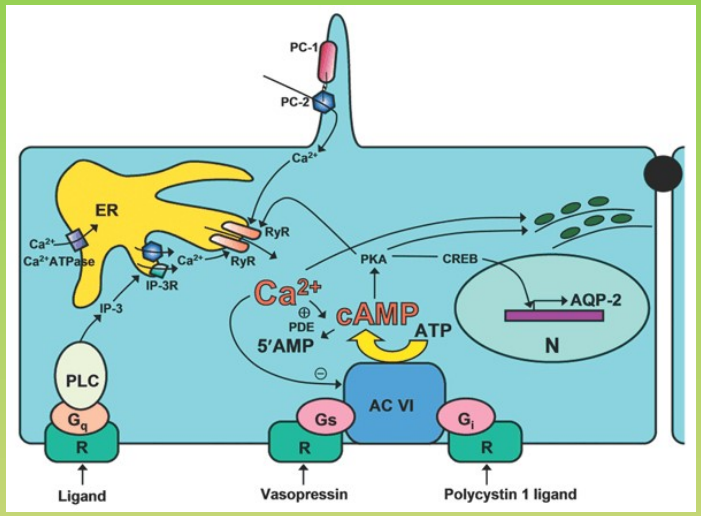




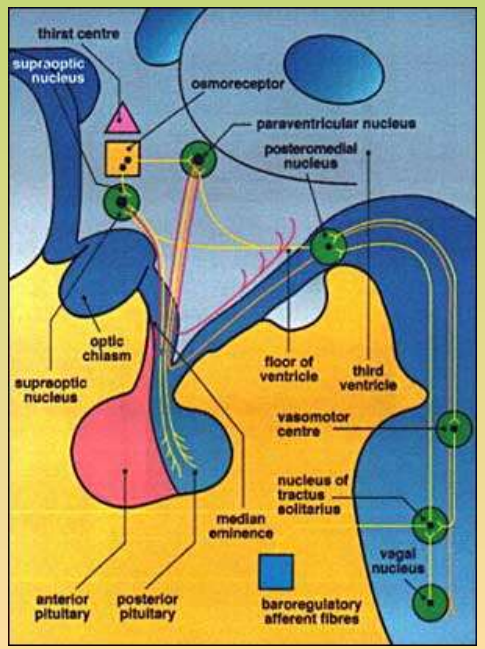


Diabetes insipidus (DI)





- (a) central DI
  - damage of >85% ADH-neurons of PVN and SON posterior pituitary = ↓ ADH
- (b) renal DI
  - caused by mutations in genes for ADH-receptors (V2) or aquaporin-2 = ↑ ADH
  - diuresis up to 20l/day (↓↓ urine osmolarity/ ↑ plasma osmolarity)
  - hypernatremia (Na >145mmol/l)
  - sensation of thirst and fluid intake may compensate D
    - But low fluid intake or low thirst sensation (hypodipsia, adipsia) dehydration threatens



SIADH

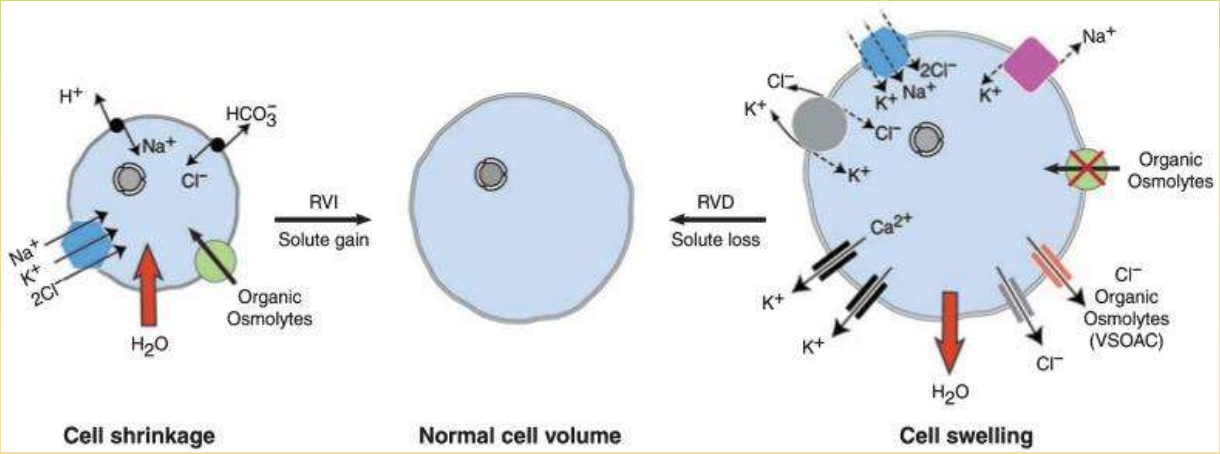
- Euvolemic/hypervolemic cancer patients have a high intracelular volume, while extracelular volume may be normal or mildly increased because of **„syndrome of inappropriate antidiuretic hormone (SIADH)“.**
- ADH promotes water uptake in the distal tubule by binding V2 receptor. Mechanism of thirst is suppressed by low osmolarity (in lab. animals, this stops the water intake, humans tend to spontaneously continue drinking even in low osmolarity).
- SIADH often develops in the tumours of lungs, pleura, brain or thymus (e.g. 10% to 45% of patients suffering from small-cell lung carcinoma have symptoms of SIADH.
- Iatrogenic causes: cytostatic drugs

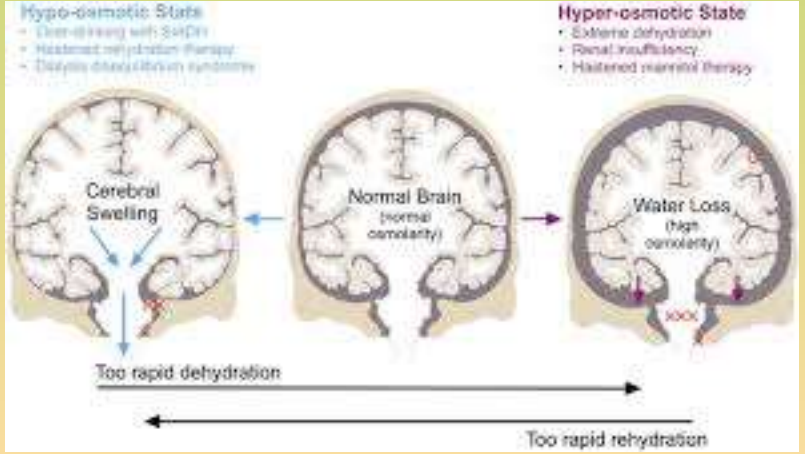
Hyper- and hypovolemia

- Hypervolemia
  - systemic edema
  - pulmonary edema
  - hypertension
- Hypovolemia
  - loss of skin turgor
  - hypotension, shock
  - renal failure (prerenal; urea:kreatinin > 100:1

Tonicity disorders and CNS

- similarly to other cells, neurons and glia swell in hypotonic solution (danger of cerebral edema) and shrink in hypertonic solution (danger of demyelination)
- in chronic conditions, neurons are able to compensate a difference in osmolariyty (tonicity) by the retention or increased removal of osmotically active solutes
- following the rapid osmolarity correction (NaCl, loop diuretics), water may be transferred in opposite direction, which threatens by opposite disorder

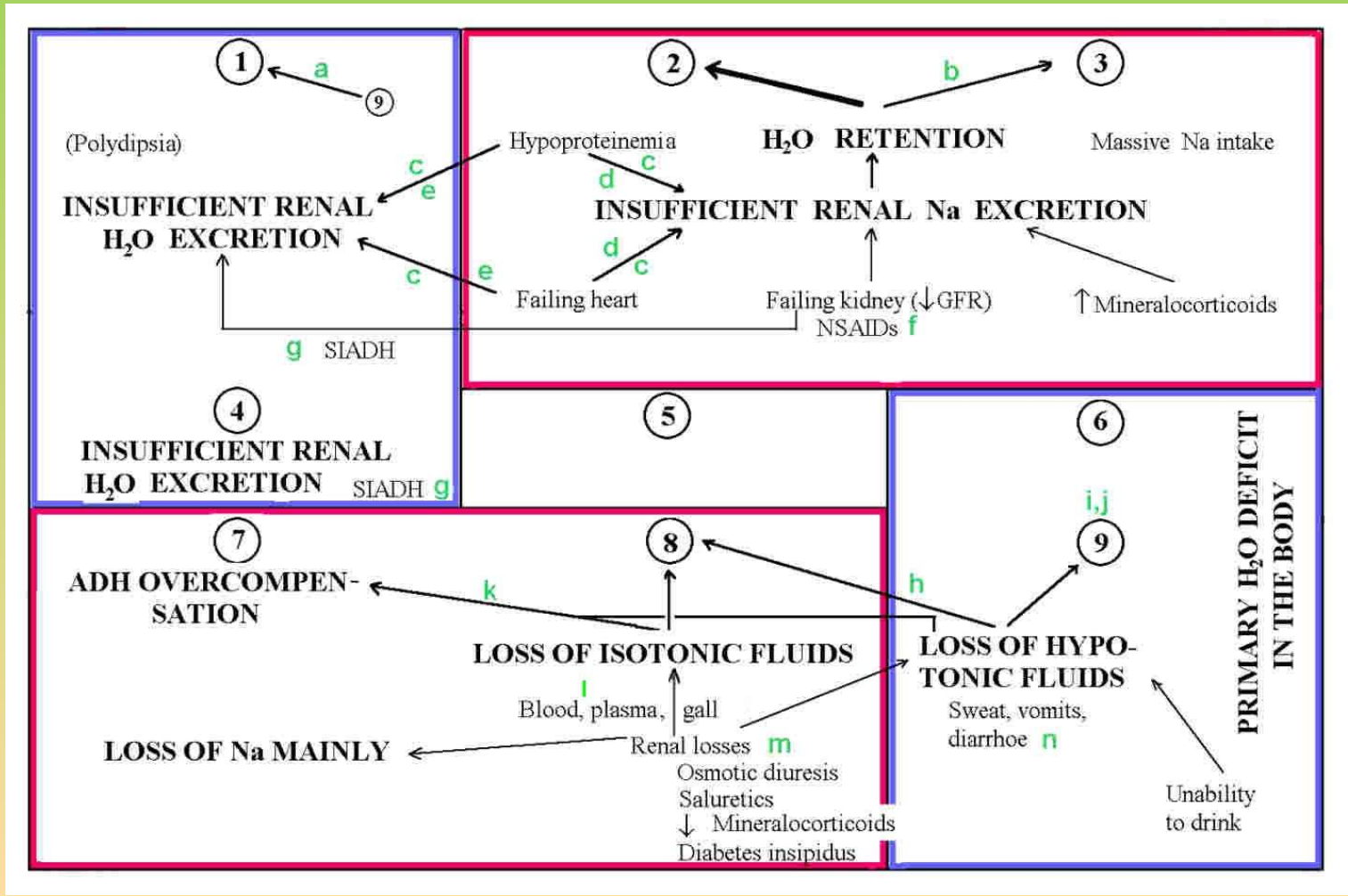




Disorders of volume and tonicity - causes

- Hypoosmolar hyperhydration
  - Psychogenic polydipsia, SIADH, glucose solutions → Glc metabolizsation
- Isoosmolar hyperhydration
  - Heart failure, kidney failure, iatrogenic – isotonic ion solutions
- Hyperosmolar hyperhydration
  - Kidney faliure, hyperaldosteronism, high NaCl intake
- Hypoosmolar dehydration
  - Addison disease, overdose by loop diuretics, lack of NaCl in food
- Isoosmolar dehydration
  - Bleeding, burns, ascites, severe (secretion) diarrhea
- Hyperosmolar dehydration
  - Low water intake, diabetes insipidus, diabetes mellitus, osmotic diuretics (manitol), diarrhea

Disorders of volume and tonicity

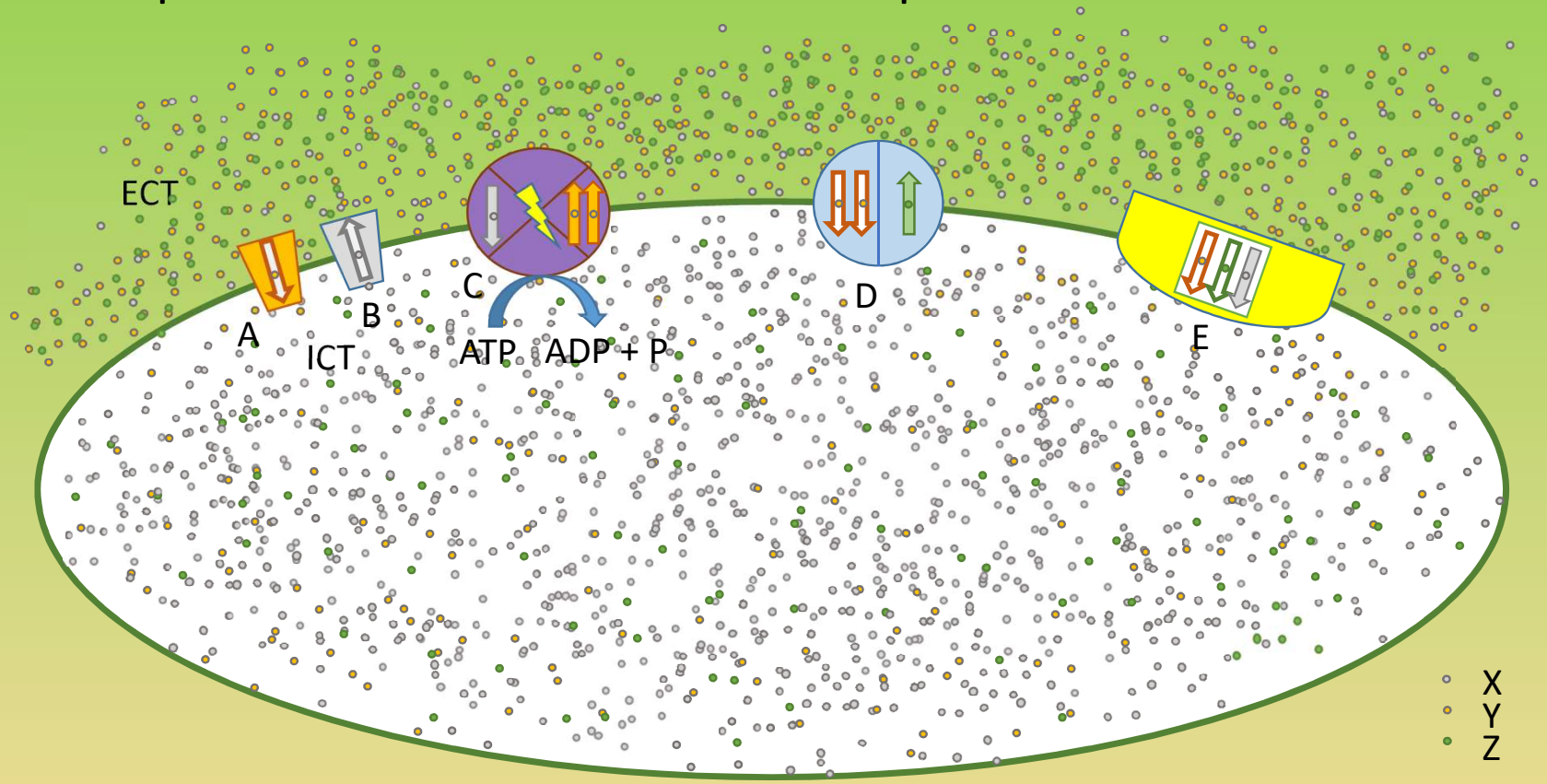


Main ions in ICF and ECF

ion	Plasma [mmol/l]	ICT [mmol/l]
Na^+	140	10
K^+	4,5	140
Ca^{2+} *	2,5	10^{-5}
Mg^{2+} *	1	8
Cl^-	100	4
$H_2PO_4^-/HPO_4^{2-}$ *	1	40
HCO_3^-	30	10

- * involves both ionized and bound form

Examples of membrane transporters



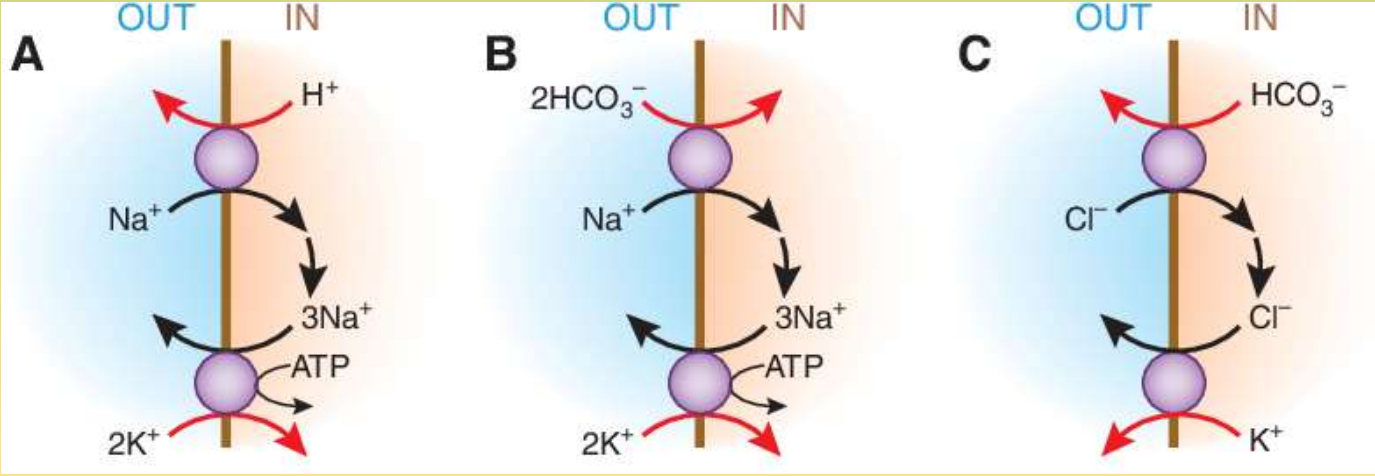
A and B are examples of membrane channels allowing the diffusion of X and Y along with their electrochemical gradients. C is an ionic pump exchanging solutes X a Y in opposite direction (which makes X an intracellular and Y an extracellular solute). D corresponds with secondary active exchanger (antiporter) changing Y ions for Z, which are thus transferred against their electrochemical gradient (a condition for this is a sufficient gradient of Y). Finally, E is a cotransporter, where Y and Z, which are transferred along with their electrochemical gradient, are accompanied by X, which goes against its gradient. This is also driven by the ionic pump creating a gradient of Y. In practice, X may be represented e.g. by potassium, Y by sodium and Z by chlorine or calcium

Potassium

- The most abundant intracellular cation (98% intracellulary)
- Most willingly passes cellular membrane
- Concentration gradient is maintained by Na+/K+ ATPase
- The extra/intracellular distribution is regulated by hormones (insulin, adrenaline, aldosterone) and pH (see further)
- Its total body content depends mainly on renal functions
- Both hyper- and hypokalemia are frequent conditions in clinical practice and both are proarrhythmogenic

Potassium and ABB

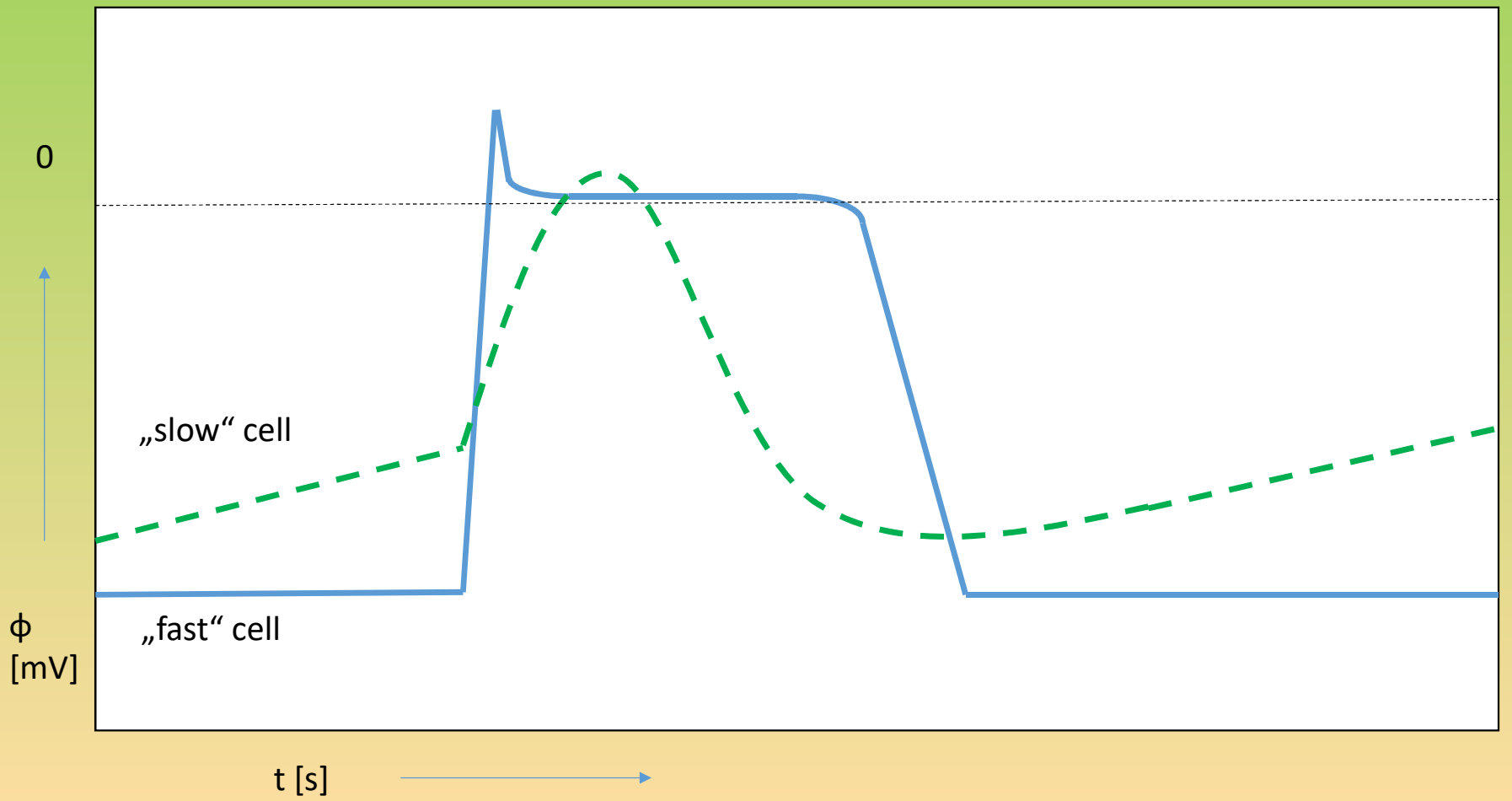
- Transcellular exchange of K^+/H^+, or eventually the $K^+ + HCO_3^-$ symport, act as a kind of buffer system allowing the binding/release of H^+ ions, while maintaining electroneutrality
- In practice, higher H^+ in the circulation is linked to K^+ transfer from the cells and vice versa
- Analogically, e.g. hypokalemia in hyperaldosteronism may lead into metabolic alkalosis
- Attention in rapid correction of ABB disorders – e.g. in chronic respiratory acidosis, kidneys compensate hyperkalemia by increased K^+ excretion; following the correction, hypokalemia may occur due to K^+ transfer inside cells (and posthypercapnic alkalosis with HCO_3^- excretion)



Potassium and the membrane potential

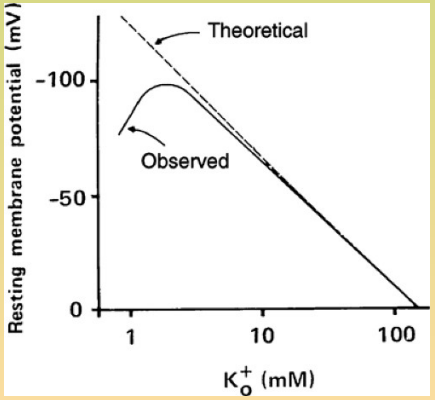
- Positively charged, intracellular ion: ↑ concentration → lowering of membrane polarity (more than corresponds with its change in ECF – analogy of a small and a large basin connected by a hose)
- Various functionally different K^+ channels
- By various mechanisms, potassium increases the permeability of K^+ channels
  - direct binding
  - competion with Mg^{2+} that closes the K^+ channels
  - changes in expression and translocation

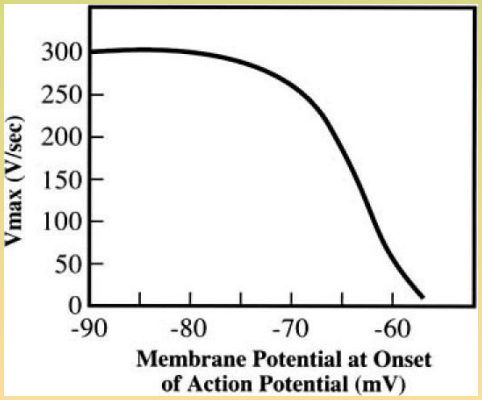
Cardiomyocyte membrane potential



Effect on sodium channels

- Mild hyperkalemia – easier excitation
- Severe hyperkalemia – block of a portion of Na^+ channel
  - Slower conduction
  - Finally the threshold voltage „runs away“ from baseline voltage and the depolarization is no longer possible
- Mild hypokalemia – hyperpolarization
- Severe hypokalemia – lack of substrate for the Na/K ATP-ase → lower polarity, easier excitation

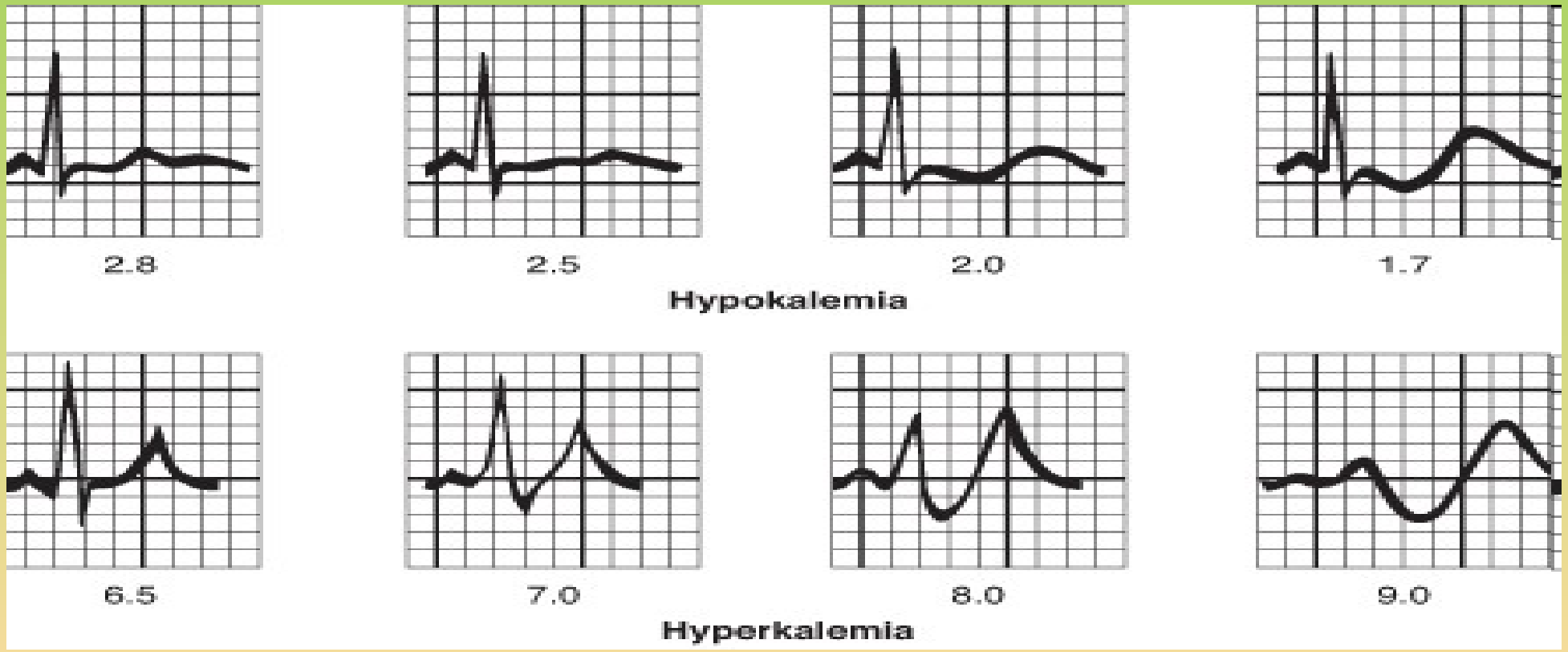




Potassium – main effects on ECG

- Hyperkalemia
  - Peaked T wave (dif. dg. hyperacute phase of MI)
  - Wide QRS (may merge into sinusoid wave with T)
  - Widening, flattening and event. disappearing of the P wave (but sinus rhythm remains for a long time)
  - Higher excitability at the beginning, then lower, diastolic arrest in the end (heart is depolarized compared to the normal state)
  - ↑ risk of re-entry (↑ differences in conduction velocities)
- Hypokalemia
  - Flat, wide T-wave
  - Pathologic U wave (delayed repolarization), lengthening of QT (QU) interval
  - EAD, torsades de pointes
  - Sometimes, peaked P is present
  - ↑ risk of re-entry (↑ differences in refraktory periods)
  - First lower excitability (hyperpolarization), then higher

Changes of ECG in hyper-/hypokalemia



Periodic muscle paralysis in hypo- and hyperkalemia

- heterogeneous group of diseases characteristic by transient attacks of muscle weakness (hours to weeks depending on type)
- usually a hereditary disease
- often caused by channelopathies (Na, K and Ca)
- secondary periodic paralysis may occur in changes of K^+ levels in both directions, thyreotoxicity (enhanced sodium-potassium pump activity)
- mediated either by hyperpolarization or by continuous depolarization of the muscle cell, which is followed by Na^+ channel deactivation
- triggering factors: K^+ or sugar intake, decrease of K^+, cold environment, muscular effort alternating with resting periods

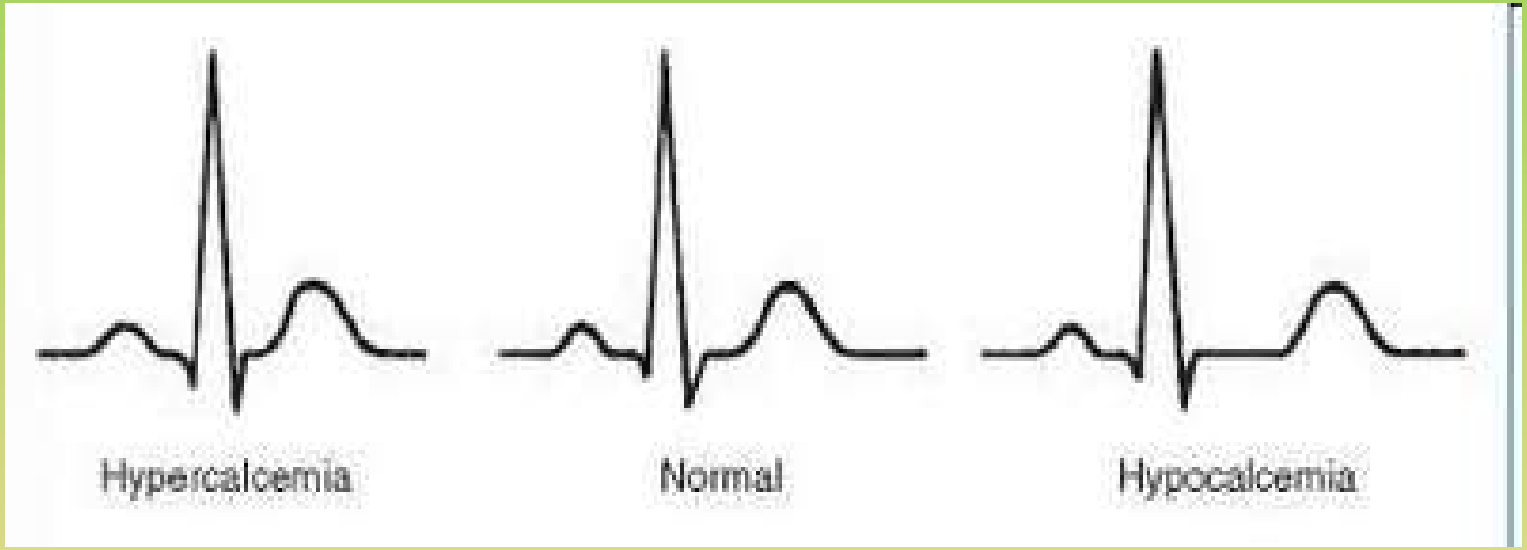
Calcium

- Ion that is necessary for muscle contraction
- Intracellulary, it is present in very low concentration (making high gradient between cytoplasm and cell)
- In cardiomyocyte and skeletal muscle, it is also present in sarcoplasmic reticulum
- Cardiomyocyte (and smooth muscle cell) bears specific Ca^{2+}-channels, that are necessary for phase 2 (plateau), pacemaker function and conduction through slow cells
- They can be blocked by specific agents to slow the heart rate and enhance vasodilatation by smooth muscle relaxation

Calcium and the membrane potential

- Extracellular ion – membrane potential gets into more negative values
  - More than expected based on the concentration, because **Ca^{2+} binds to phospholipid bilayers and tends to concentrate in their proximity**
- During the action potential, Ca^{2+} activate potassium (and chloride) channels, which shortens the phase 2 → repolarization leads into the closing of Ca^{2+} L-channels
  - the proces is impostant for maintaining the calcium homeostasis in the cell
  - in extreme hypercalcemia, phase 2 may be missing
  - opposite effect may be present in hypocalcemia
- Mechanical effects
  - Extreme hypercalcemia: triggered activity (DAD), systolic arrest (very rare)
  - Extreme hypocalcemia: triggered activity (EAD), hypocalcemic cardiomyopathy, heart failure

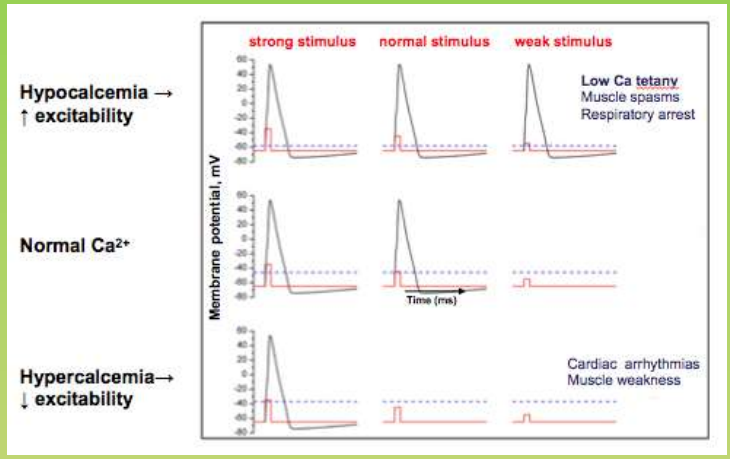
ECG in calcium levels changes

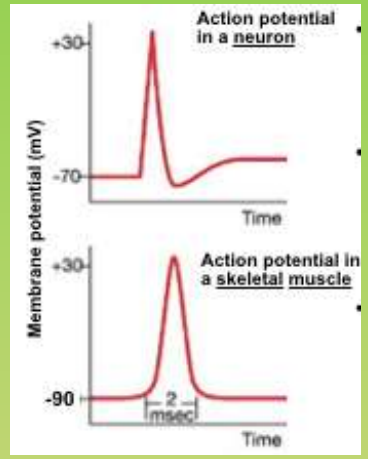


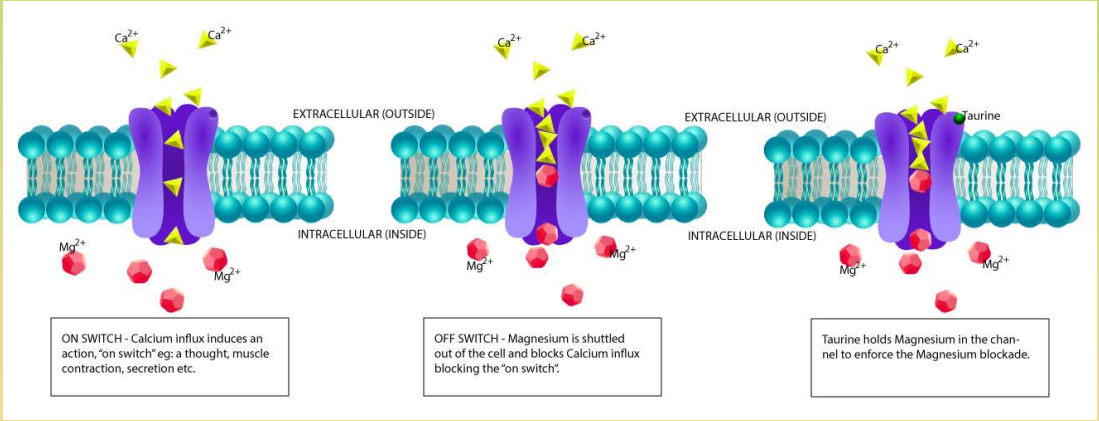
- The Ca2+ channels-blockers mainly induce the conduction (SA or AV) node blocks and slower pacemaker function

Calcium and tetany

- Physiologically, neurons have lower difference between resting and threshold membrane potential compared to myocytes
- When Ca^{2+} decreases, membrane potential locally shifts to more positive values, which leads into neuronal and muscular depolarizations
- Skeletal muscle cell has a short refractory period and the contraction starts after its end – new activation may thus occur during the contraction
- This leads into the summation of muscle contractions
- Tetany also occurs in alkalosis, when ionized Ca^{2+} decreases (Ca^{2+} competes with H^+ for protein binding), or in $\downarrow Mg^{2+}$, when Ca^{2+} decreases in the ECF (both locally and systemically ↓PTH)
- In hypercalcemia, excitability decreases with hyporeflexia or even coma (similarly to acidosis and $\uparrow Mg^{2+}$)

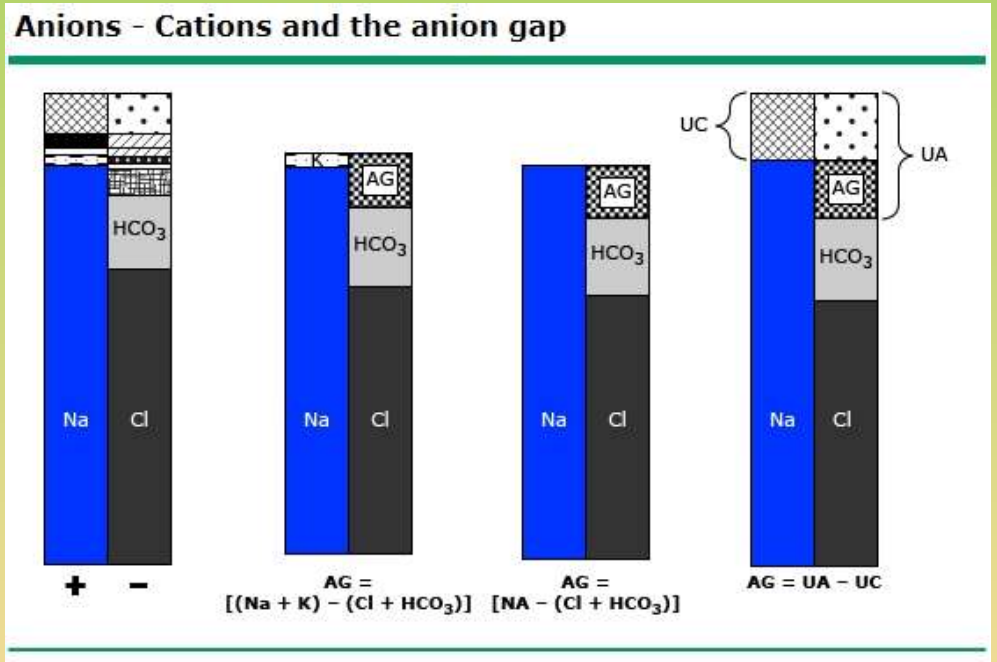






Chlorine and ABB

- Electroneutrality principle: positive charge in plasma = negative charge
- Cationic side: Na^+, K^+, Ca^{2+}, Mg^{2+}
  - Relative fixed, rather long-term regulation
- Anionic side: Cl^-, HCO_3^-, proteins, fixed acids
  - Strong link to AB
- Chlorine itself is fully ionized in the water solution and does not act as either donor or acceptor of H^+
  - but **HCO_3^- and fixed acids (part of anion gap) do**



Hyper- a hypochloremia

- Is not a problem itself, Na^+ and HCO_3^- levels are key
- If the changes of Cl^- levels are accompanied by corresponding adequate changes of Na^+ in the same direction → osmolarity disorder
  - E.g. loss of net water, DI × SIADH
  - HCO_3^- and anion gap do not change
- On contrary „pure“ change of Cl^- (without Na^+) is always accompanied with changes of other anions
- „Pure“ hypochloremia → ↑HCO_3^- , metabolic alkalosis
  - Mental bulimia, secretion diarrhea with high losses of Cl^-, Bartter syndrome in low renal $Na^+/K^+/2Cl^-$ cotransporter aktivity
- „Pure“ hyperchloremia → ↓HCO_3^- , metabolic acidosis
  - Rapid administration of hyperchloremic saline solution („physiologic saline“ has 154 mmol/l of both Na^+ and Cl^-, Cl^- thus increases more rapidly than Na^+)

JM1

JM1 Jan Máchal; 29.05.2024

Secondary „pure“ hyper- and hypochloremia

- „evens up“HCO_3^- or anion gap changes (electroneutrality principle)
- Hyperchloremia
  - Renal tubular acidosis –HCO_3^- losses
  - Hyperparathyreosis – losses of the phosphate anion
- Hypochloremia
  - Posthypercapnic alkalosis following the rapid correction of chronic respiratory acidosis (↑HCO_3^-)
  - Diabetic ketoacidosis – increase of ketone bodies (part of anion gap) with both Cl^- and HCO_3^- losses