Integrated pathophysiology of fluid, osmolality, electrolyte and pH homeostasis (ABB) – part 1

Summary of basic facts - water balance in human body

Volume – osmolality relationship and its changes

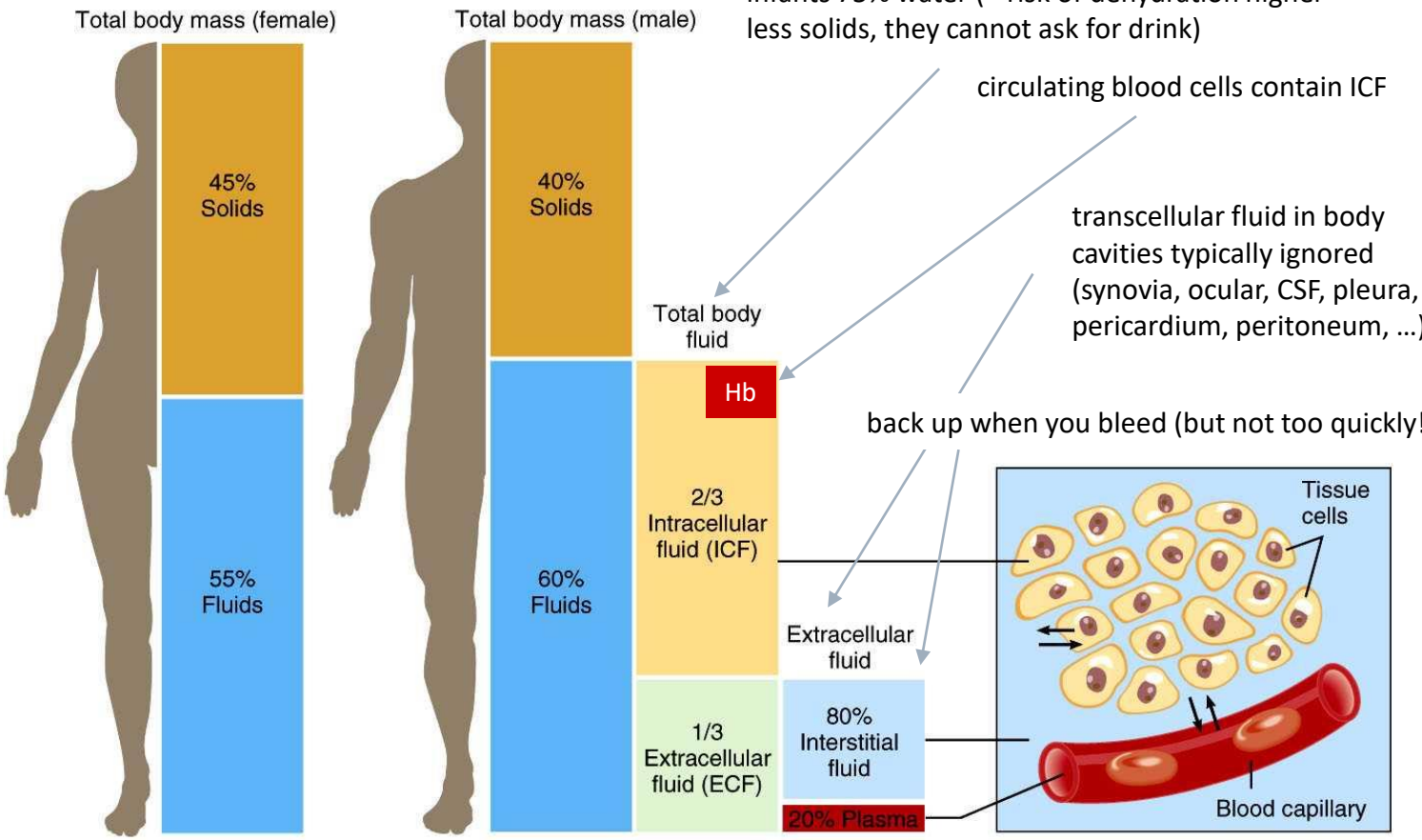
Regulation of ABB

Overview of disease impairing V-O matching

Pathophysiology of clinically important disorders affecting V-O as well as ABB

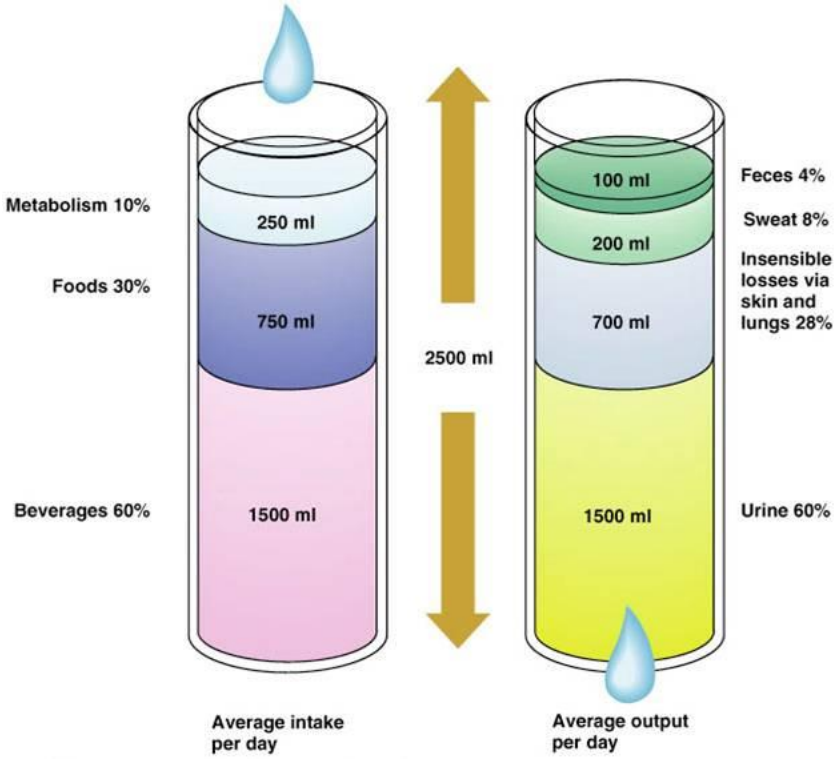
BODY FLUIDS AND THEIR COMPOSITION

Body fluid compartments

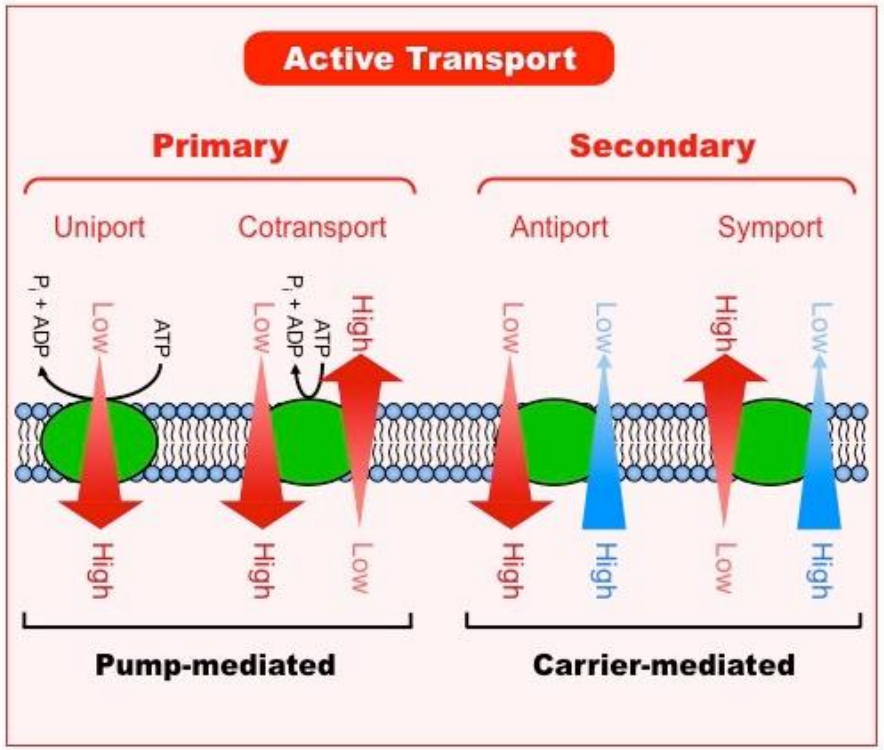


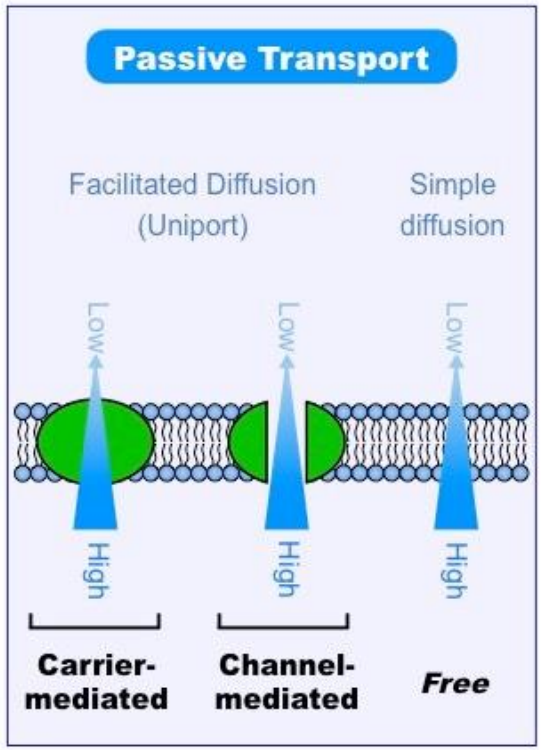
- infants 75% water (= risk of dehydration higher – less solids, they cannot ask for drink)
- circulating blood cells contain ICF
- transcellular fluid in body cavities typically ignored (synovia, ocular, CSF, pleura, pericardium, peritoneum, …)
- back up when you bleed (but not too quickly!!!)

- water is special and excellent!
  - very high specific heat (boils and freezes at extremes)
  - capillary action
    - helping many processes (vessels, breast-feeding, lacrimation, …)
  - perfect solvent
  - participates in redox reactions (give rise to ROS)
- processes gaining and loosing water

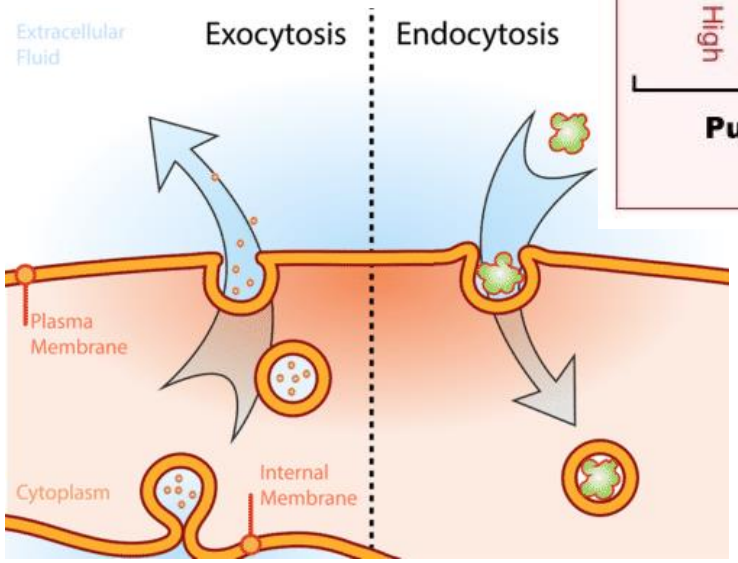


Membrane defines the compartments - transport





O_2, CO_2, urea, water (osmosis) through membrane (slow) or aquaporins (fast)

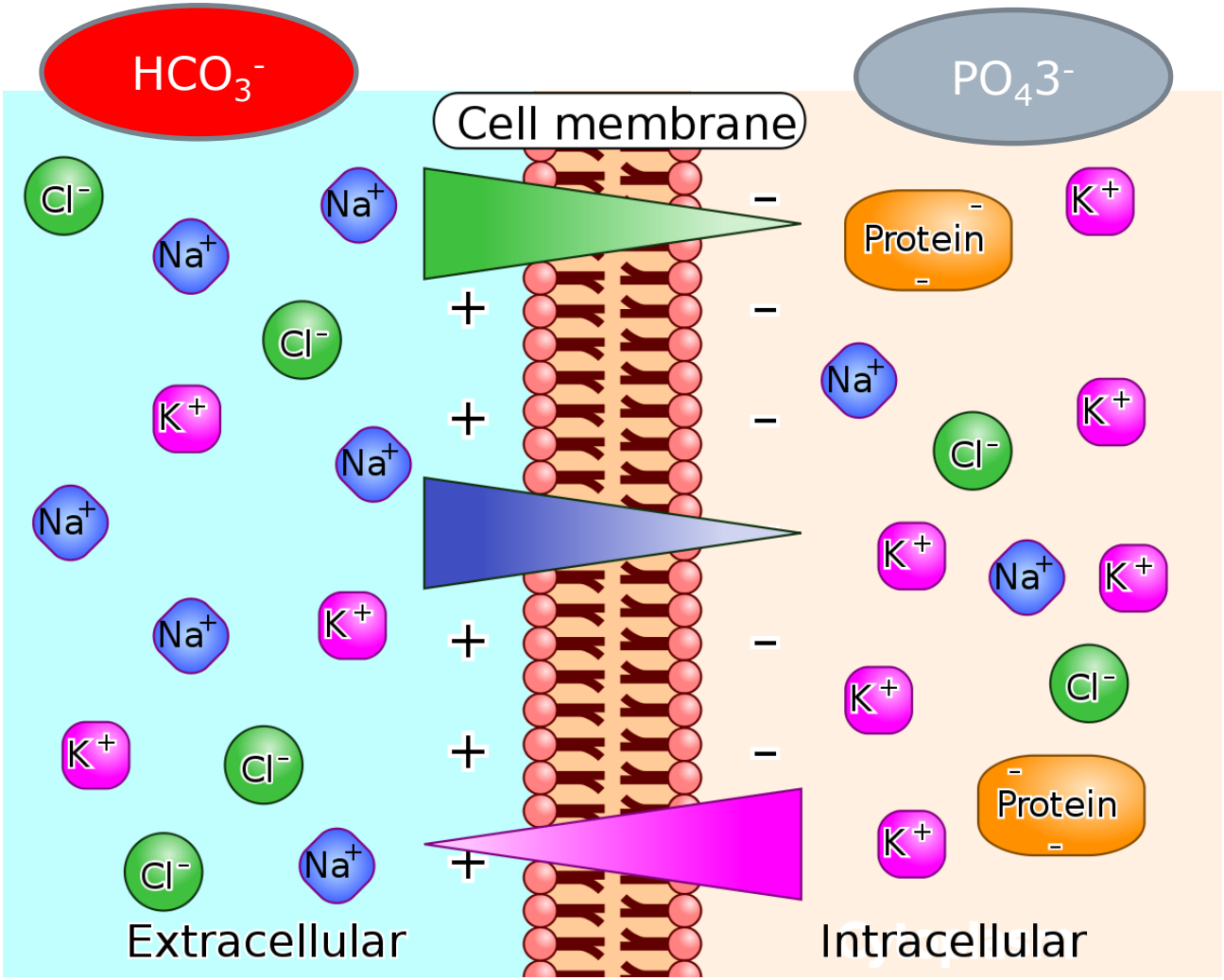


many types of ATP-ases (Na-K every cell, H^+in kidney, Ca^{++} in muscle, K^+-H^+ stomach proton pump]

structural specificity, competition, saturation

ligand (cAMP, hormone) vs. voltage gated

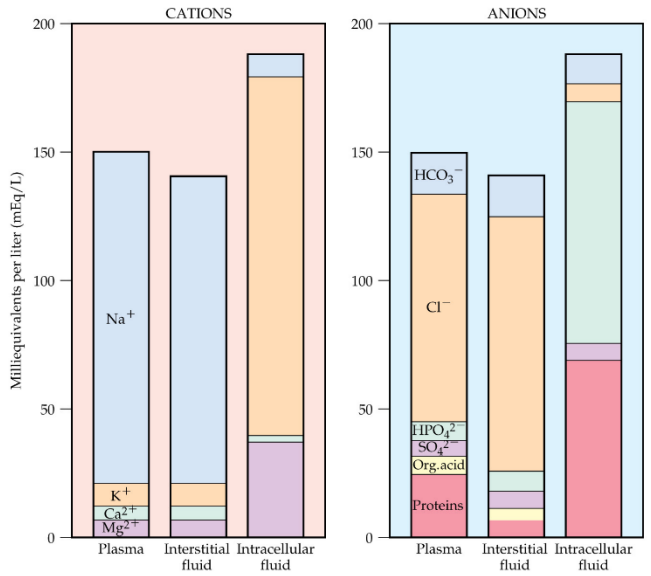
Electrolyte balance ICT/ECT – why like that?

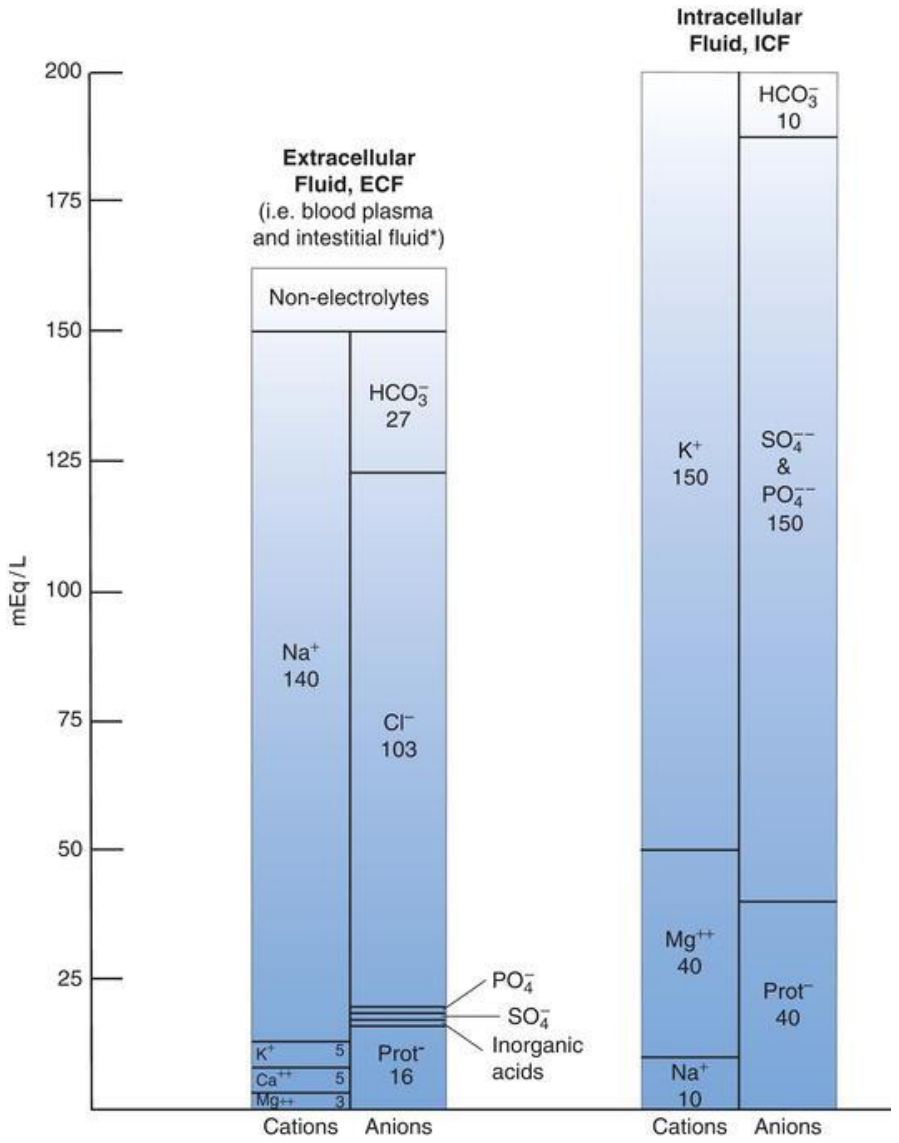


- activity of Na/K ATPase
- selective permeability of K^+
- proteins kept inside
  - majority of body protein is intracellular
- Cl^- follows the Na^+
- phosphate has a gradient (consumed) inside since necessary for
  - production of ATP
  - phosphorylation by kinases
  - making Glu-6-P
    - clinical example: refeeding syndrome (e.g. in anorexia nervosa patients)
- hydrogencarbonate establishes the alkaline reserve
  - because the metabolism (happening inside the cell) produces lots of acids (that will eventually leave cell), plasma retains „alkaline reserve" to buffer

The law of electroneutrality

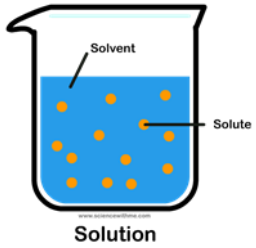
- in any electrolyte solution the sum of positive charges equals to the sum of negative ones
- Right: mEq/L = mmol/L for monovalent ions (e.g. Na and K) but mEq/L must be divided by 2 to convert mmol/L for divalent ions (e.g. Ca and Mg)
  - figures for ECF refer specifically to blood plasma; interstitial fluid very similar except it has lower protein and higher chloride concentration.

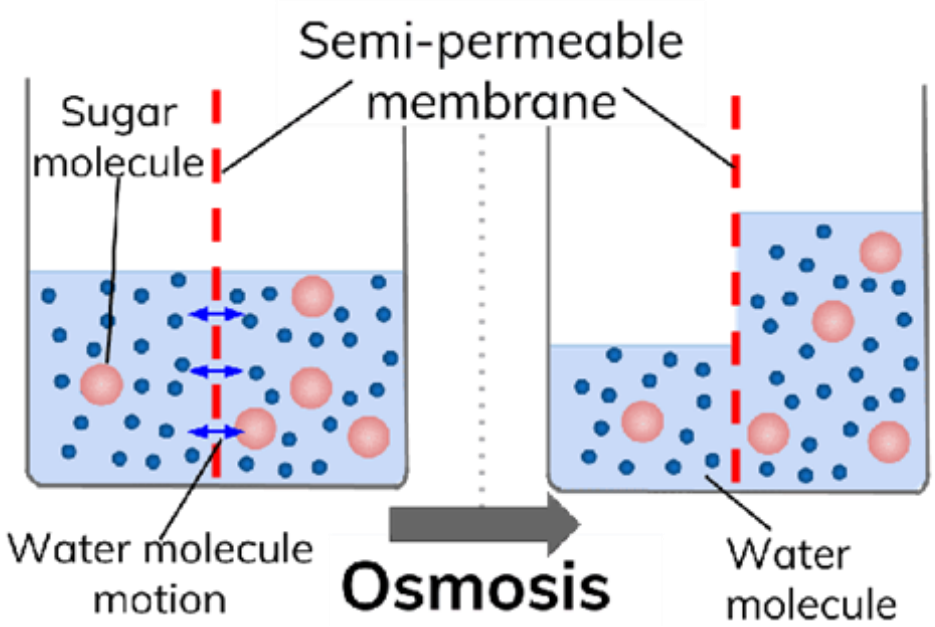


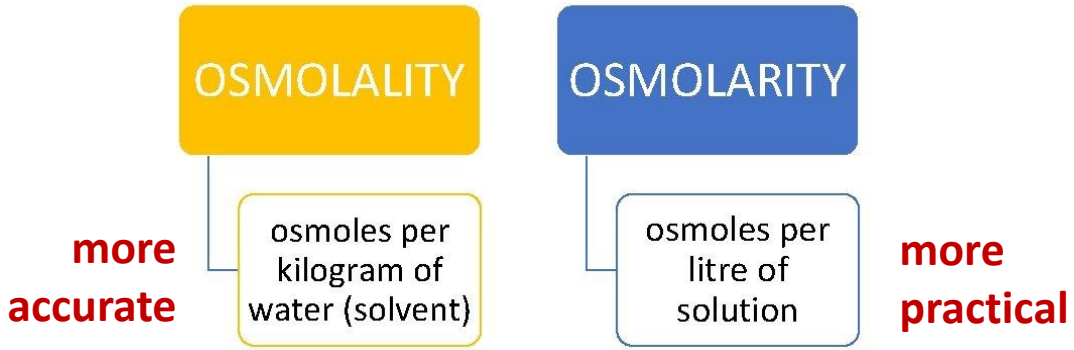


Osmosis, osmolality & osmotic pressure

- osmosis – a type of passive membrane transport
  - movement of water from its high concentration (= low concentration of solutes) to low concentration (= high concentration of solutes)
- osmolality it is about <u>number</u> of molecules (not size or mass)
  - 1mol Glu → 1 osmol
  - 1mol Cl_2 → 2 osmoles (Cl^- + Cl^-)
- osmotic pressure
- measured vs. calculated osmolality
  - measured by osmometer
  - calculated 2xNa^+ + Glu/20 + BUN/3 = 290 mOsm/L
    - only Na and glucose represent <u>effective osmolality</u>
      - ☛ BUN freely diffuses across the membrane
    - normal interstitium = plasma = ICF
    - the difference between m and c = **osmolar gap**
      - ☛ normally ≤10
      - ☛ if >10 then other molecules present (methanol, ethanol, ethylene glycol (all 3 causing HAGMA), sorbitol, mannitol, drugs, …)

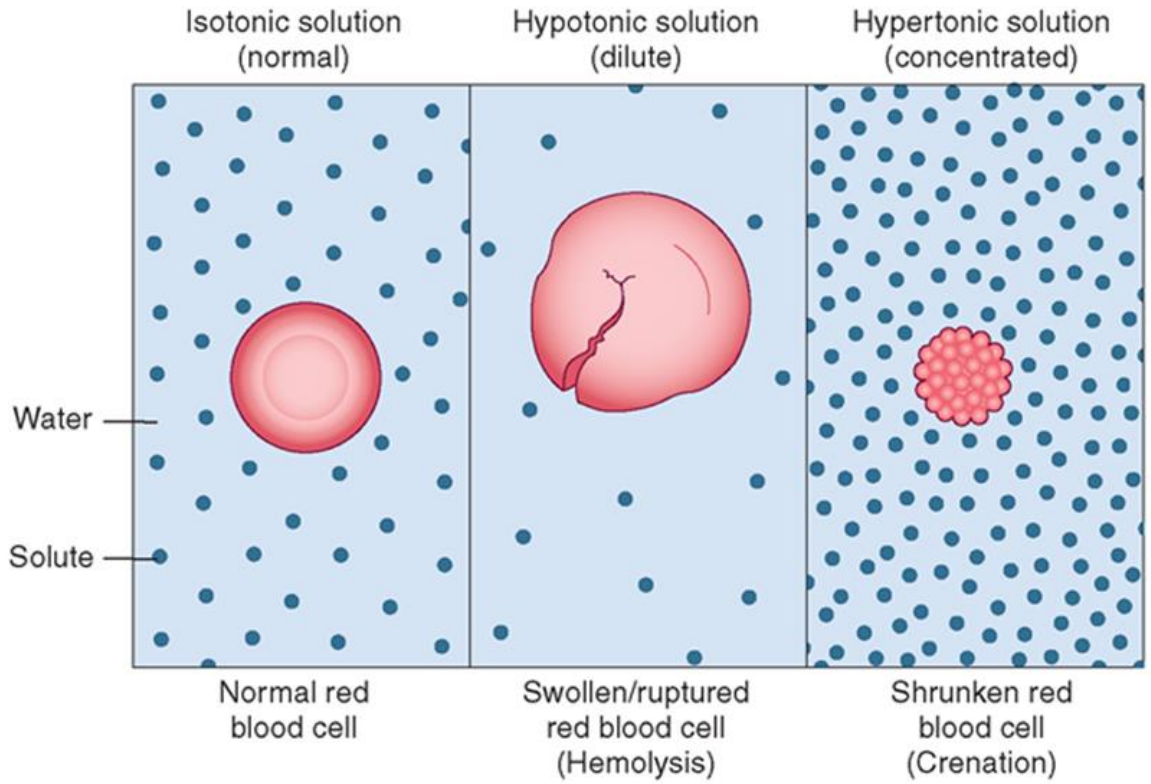




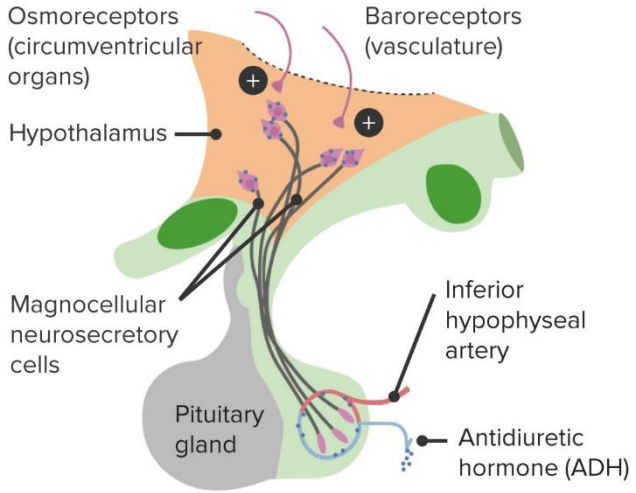


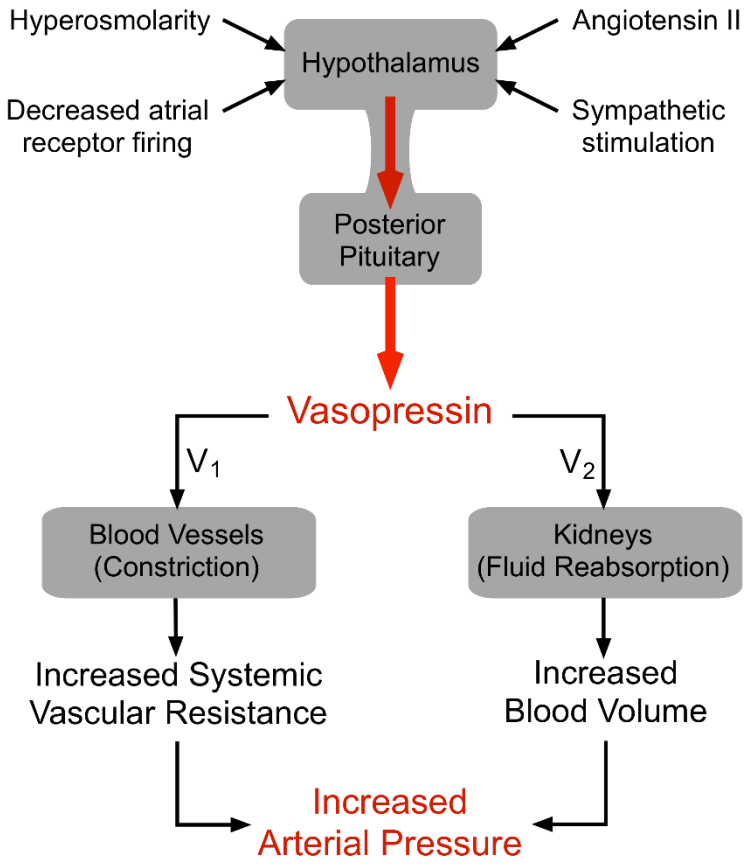
Osmolality vs. tonicity (made simple)

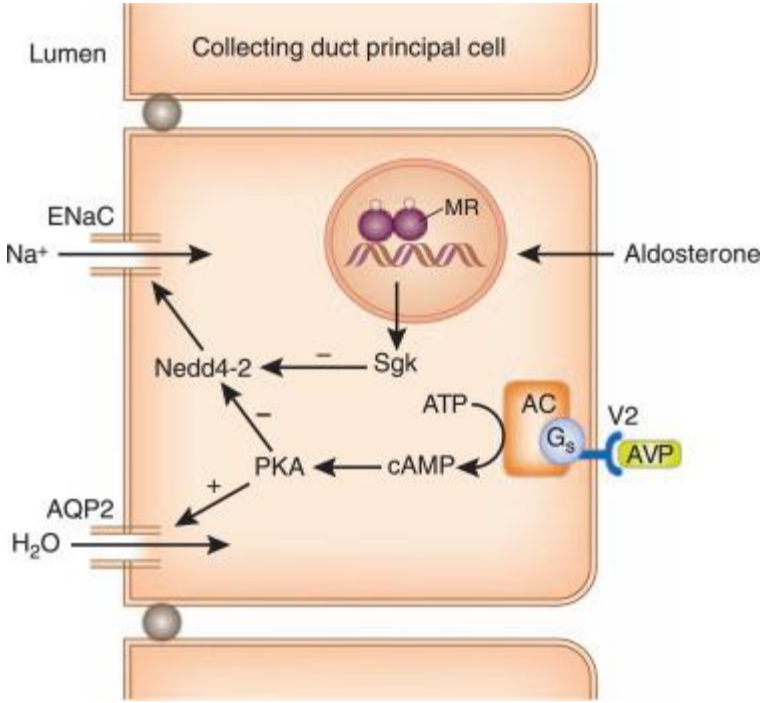
- osmolality = the total number of osmoles in given volume of water
- tonicity = only considers <u>effective osmoles</u> (cannot cross the plasma membrane) in a volume of water
  - describes osmotic pressure <u>gradient</u>
  - describes osmolality of the solution <u>relative to plasma</u>
    - isotonic 290 [275 - 295]
    - hypotonic <275
    - hypertonic >295
- **hypertonicity** stimulates the **thirst** and **ADH release**



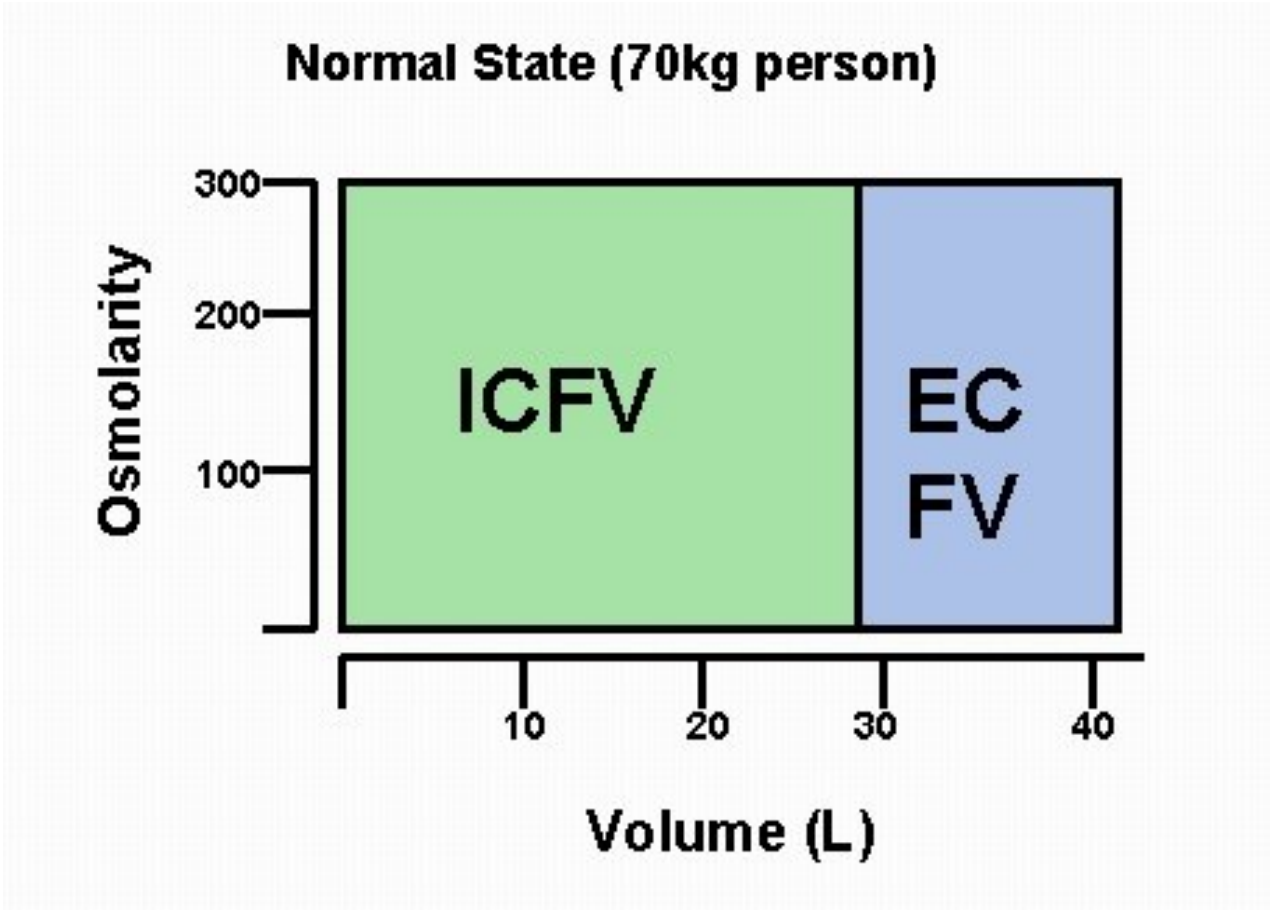
ADH/arginine-vasopressin





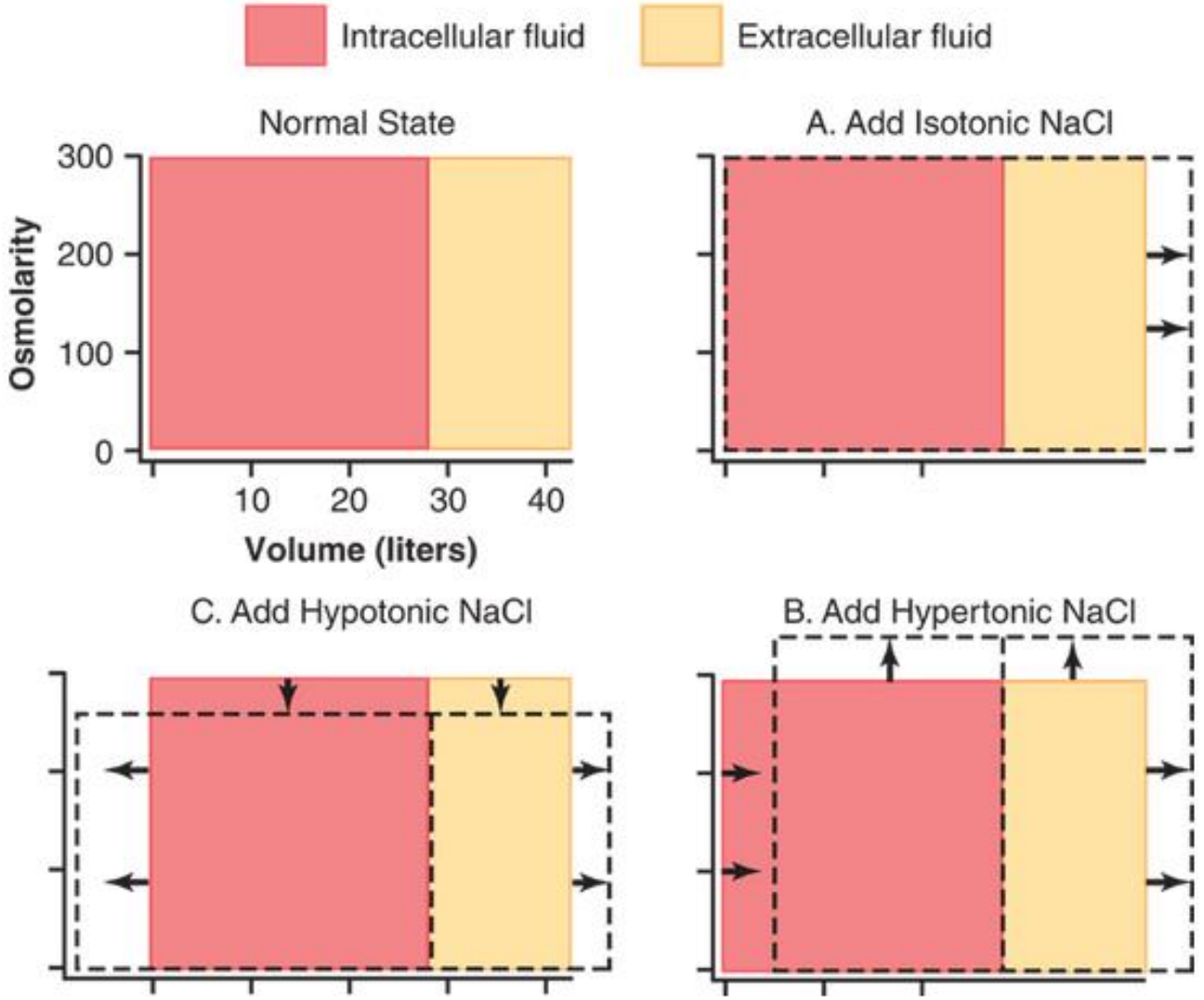


Volume – osmolality diagram

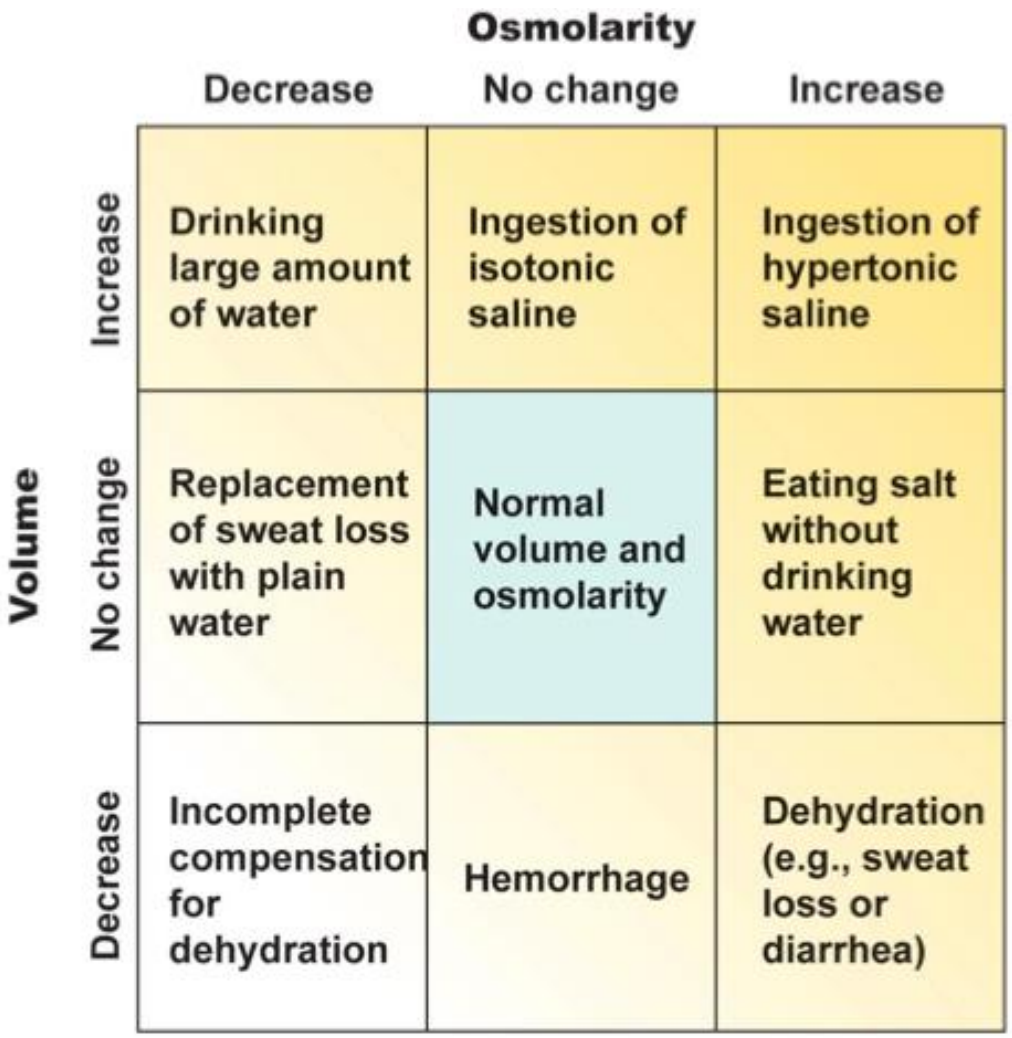


Why is this important? for infusion of solutions (crystalloids) to patients

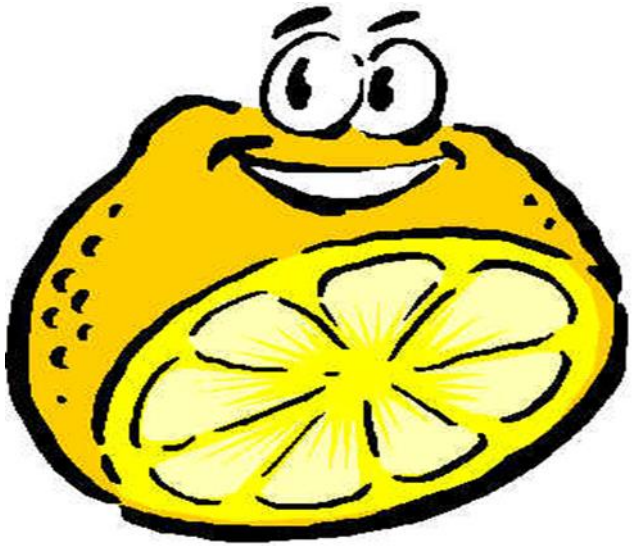
- 60% of TBW
  - 40% ICF
  - 20% ECF
    - 5% plasma
    - 15% ISF
      - ☛ 1:3 ratio!!!
- effect of adding different solutions to ECF



How to approach volume-osmolality balance problems?



- does the situation affects?
  - (1) ECF volume change?
  - (2) ECF osmolality change?
    - no
    - yes (3) ICF volume and osmolality
      - ☛ water will move by osmosis and the two compartments will gradually equilibrate



BODY FLUIDS AND THEIR COMPOSITION

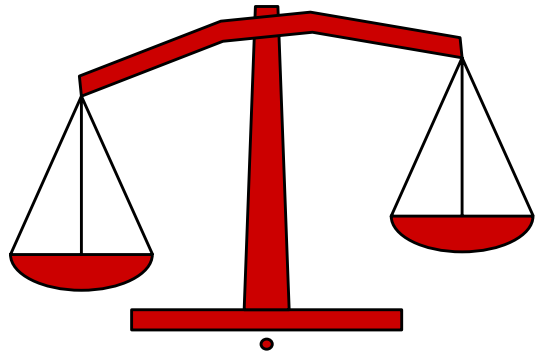
Acids vs. Bases

- definition: Bronsted-Lowry (1923)

Acid: H^+ donor
Base: H^+ acceptor

- normal A:B ratio ~ 1:20

Henderson-Hasselbach equation:
$pH = 6.1 + \log([HCO_3^-] / 0.03\ pCO_2)$



- strength is defined in terms of the tendency to donate (or accept) the hydrogen ion to (from) the solvent (i.e. water in biological systems)

pH

- amount of H^+ in the blood is routinely expressed as a pH rather than absolute concentration in mmol/l because this is ~ million-times lower than for common electrolytes (e.g. Na^+, K^+, Ca^{++}, …)
  - pH is thus an indirect measure of $[H^+]$
    - pH 7 = 1×10^{-7} (= 0.0000001) mmol/l

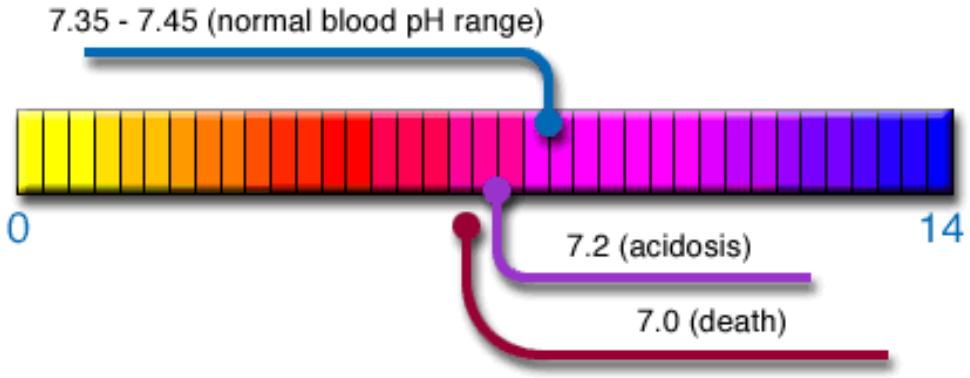
      ☛ CAVE! Hydrogen ions (i.e. protons) do not exist free in solution but are linked to adjacent water molecules by hydrogen bonds (H_3O^+)

  - ↑$[H^+]$ by a factor of 2 causes a ↓ pH of 0.3

$$pH = -\log [H^+]$$

pH 7.40 ~ 40 nM
pH 7.00 ~ 100 nM
pH 7.36 ~ 44 nM
pH 7.44 ~ 36 nM

- neutral vs. normal plasma pH
  - pH 7.4 (7.36-7.44) → normal
  - pH 7.0 → neutral but fatal!!!



Why is pH so important ?

- $[H^+]$ ~ nmol/l, $[K^+, Na^+, Cl^-, HCO_3^-]$ ~ mmol/l; however, $[H^+]$ is crucial:
  - pH affects function of proteins
    - hydrogen bonds = 3-D structure = function
  - All the known low molecular weight and water soluble biosynthetic intermediates possess groups that are almost completely ionised at neutral pH'
    - pH-dependent ionisation (i.e. charge) serves to an efficient intracellular trapping of ionised compounds within the cell and its organelles
- Exceptions:
  - macromolecules (proteins)
    - mostly charged anyway or size-trapping or hydrophobic
  - lipids
    - those needed intarcellularly are protein-bound
  - waste products
    - excretion is desirable

The most important pH for the body is the intracellular pH

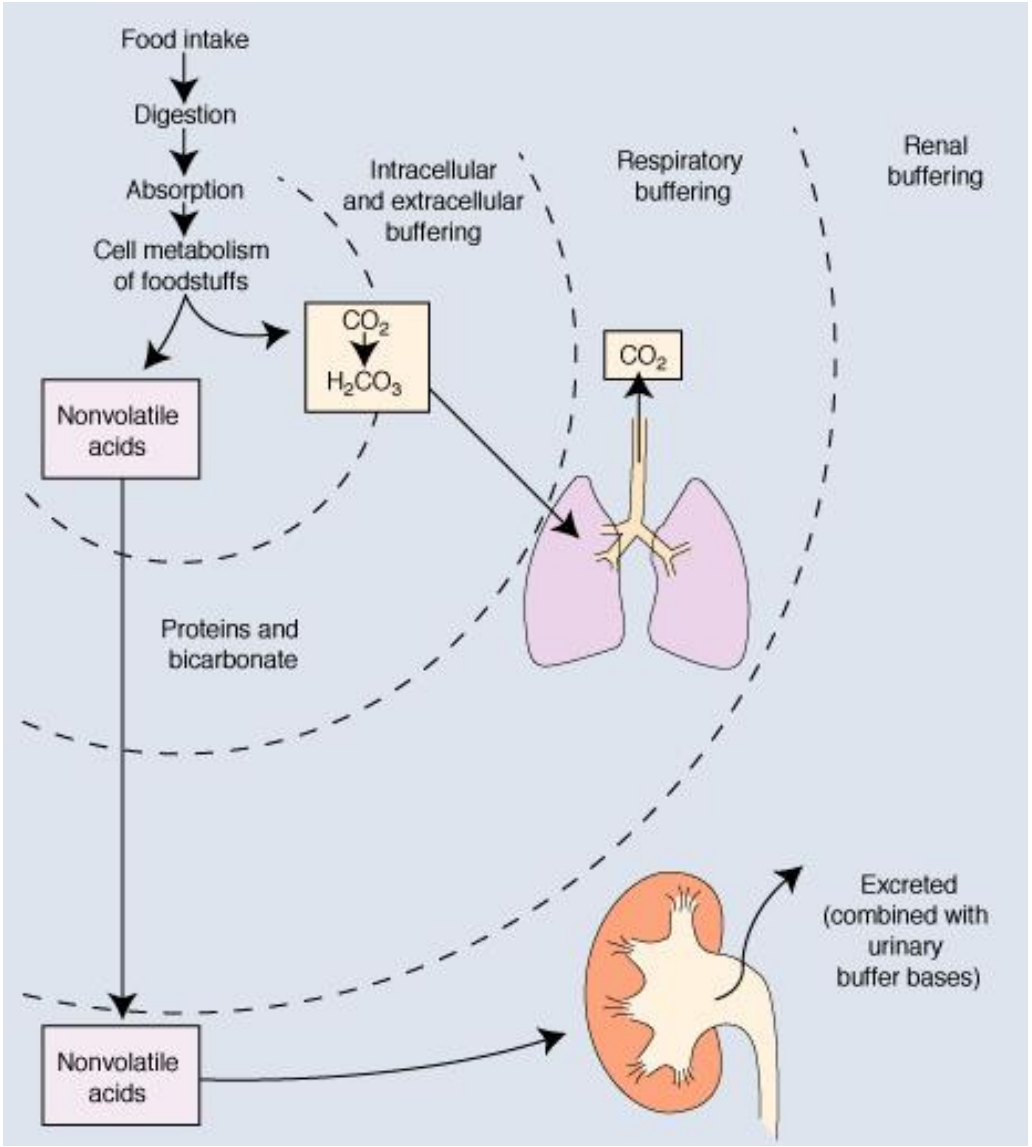
- Intracellular pH is maintained at about the pH of neutrality (~6.8 at 37°C) because this is the pH at which metabolite intermediates are all charged and trapped inside the cell

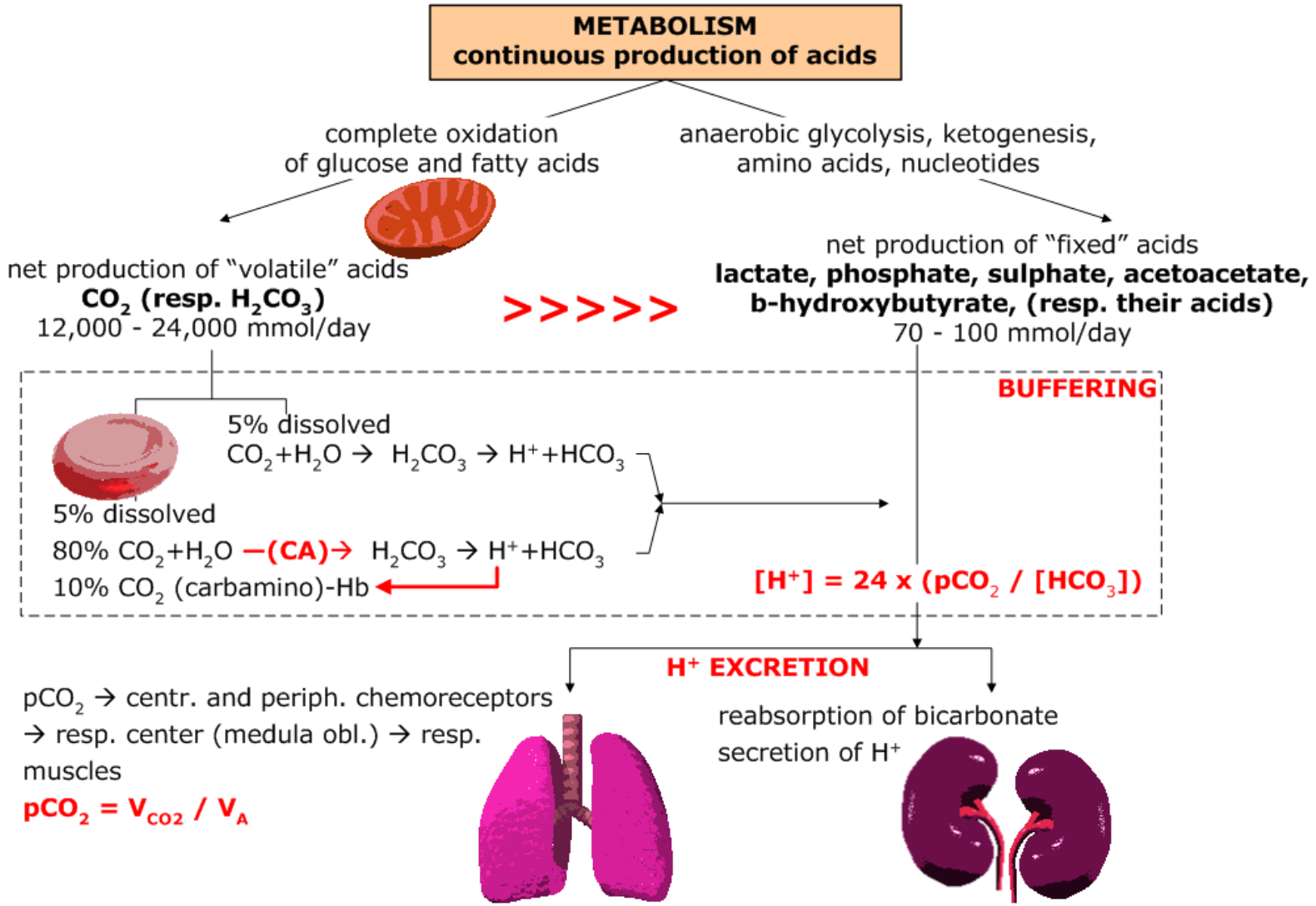
pN → $[H^+] = [OH^-]$
pN=7.0 at 25°C for pure H_2O
pN=6.8 at 37°C in cell

- Extracellular pH is higher by 0.5 to 0.6 pH units and this represents about a 4-fold gradient favouring the exit of hydrogen ion from the cell
  - ☛ to maintain it at a stable value because of the powerful effects of intracellular [H+] on metabolism
- maintaining a stable intracellular pH by:
  - 'Intracellular buffering' (chemical, metabolic, organelles)
  - Adjustment of arterial pCO_2
  - Loss of fixed acids from the cell into the extracellular fluid

pH is constantly "impaired" by metabolism

- production of metabolic acids
  - **"volatile" acids** (CO_2 resp. H_2CO_3)
    - intermediate metabolism of substrates (oxidation)
      - ☛ $CO_2 + H_2O \rightarrow H_2CO_3$
  - **"fixed" acids**
    - strong anorganic acids
      - ☛ metabolism of proteins resp. AA
        - sulphuric (Met, Cys)
        - hydrochlorous (Arg, Lys)
      - ☛ metabolism of nucl. acids
        - phosphoric (DNA)
    - lactate
      - ☛ anaerobic glycolysis
    - keton bodies
      - ☛ metabolism of fatty acids → ketogenesis → acetoacetate and hydroxybutyrate
- regulation of pH
  - intracell. a extracell. buffers
  - lungs - respiration (CO_2)
  - kidneys
    - reabsorption of HCO_3^-
    - excretion of H^+

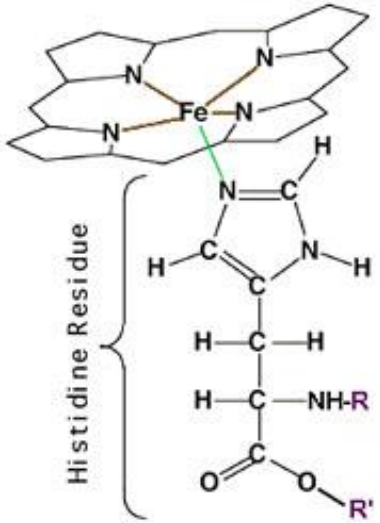


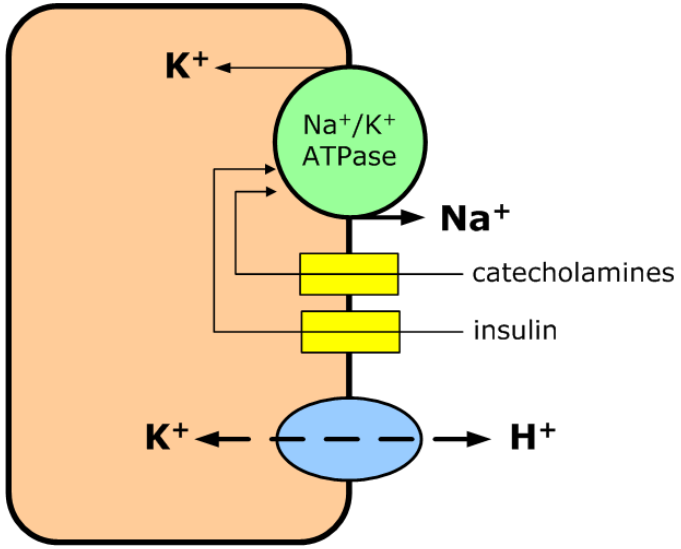

METABOLISM
continuous production of acids
complete oxidation
of glucose and fatty acids
anaerobic glycolysis, ketogenesis,
amino acids, nucleotides
net production of "volatile" acids
CO2 (resp. H2CO3)
12,000 - 24,000 mmol/day
>>>>>
net production of "fixed" acids
lactate, phosphate, sulphate, acetoacetate,
b-hydroxybutyrate, (resp. their acids)
70 - 100 mmol/day
BUFFERING
5% dissolved
CO2+H2O → H2CO3 → H+ +HCO3
5% dissolved
80% CO2+H2O —(CA)→ H2CO3 → H+ +HCO3
10% CO2 (carbamino)-Hb
[H+] = 24 x (pCO2 / [HCO3])
H+ EXCRETION
pCO2 → centr. and periph. chemoreceptors
→ resp. center (medula obl.) → resp.
muscles
pCO2 = VCO2 / VA
reabsorption of bicarbonate
secretion of H+

Chemical buffers and other types of H^+ buffering

- (1) proteins (☝ amphoteric)
  - H^+ and CO_2 diffuse across plasma membrane and are buffered
  - ECF - albumin
    - haemoglobin is strictly speaking ICF, but..!!
  - ICF – cellular proteome
- (2) inorganic buffers
  - ECF - carbonic acid / bicarbonate
    - H_2CO_3 / HCO_3^-
  - ICF - phosphoric acid / hydrogen phosphate
    - H_3PO_4 / $H_2PO_4^-$ + HPO_4^{2-}
- (3) transcellular exchange H^+/K^+
  - **changes of ABB influence potassium balance and vice versa !!!**
  - hormonal effects!!

Henderson-Hasselbalch equation:
$pH = 6.1 + \log([HCO_3^-] / 0.03\ pCO_2)$

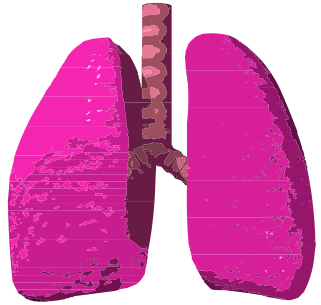




Organs involved in the regulation of ABB

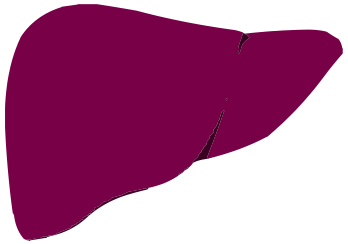
- Equilibrium with plasma
- High buffer capacity
  - Haemoglobin – main buffer for CO_2

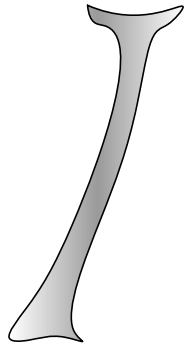
- Excretion of CO_2 by alveolar ventilation: minimally 12,000 mmol/day
- Respiratory centre react in minutes, maximum of compensation in 12 – 24 hod, then decline of sensitivity



- Reabsorption of filtered bicarbonate: 4,000 to 5,000 mmol/day
- Excretion of the fixed acids (acid anion and associated H^+)
  - about 100 mmol/day

- CO_2 production from complete oxidation of substrates
  - 20% of the body's daily production
- Metabolism of organic acid anions
  - such as lactate, ketones and amino acids
- Metabolism of ammonium
  - conversion of NH_4^+ to urea in the liver consumes HCO_3^-
  - production of glutamate = urine buffering
- Production of plasma proteins
  - esp. albumin contributing to the anion gap



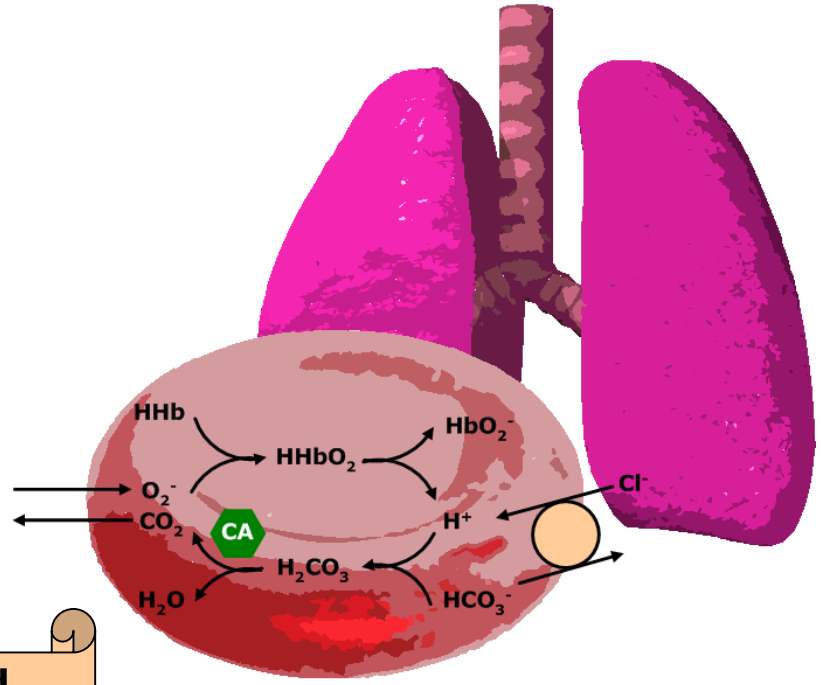


- Bone inorganic matrix consists of hydroxyapatite crystals ($Ca_{10}(PO_4)_6(OH)_2$]
  - bone can take up H^+ in exchange for Ca^{2+}, Na^+ and K^+ (ionic exchange)
  - release of HCO_3^-, CO_3^- or HPO_4^{2-}

Regulation by resp. system - CO_2

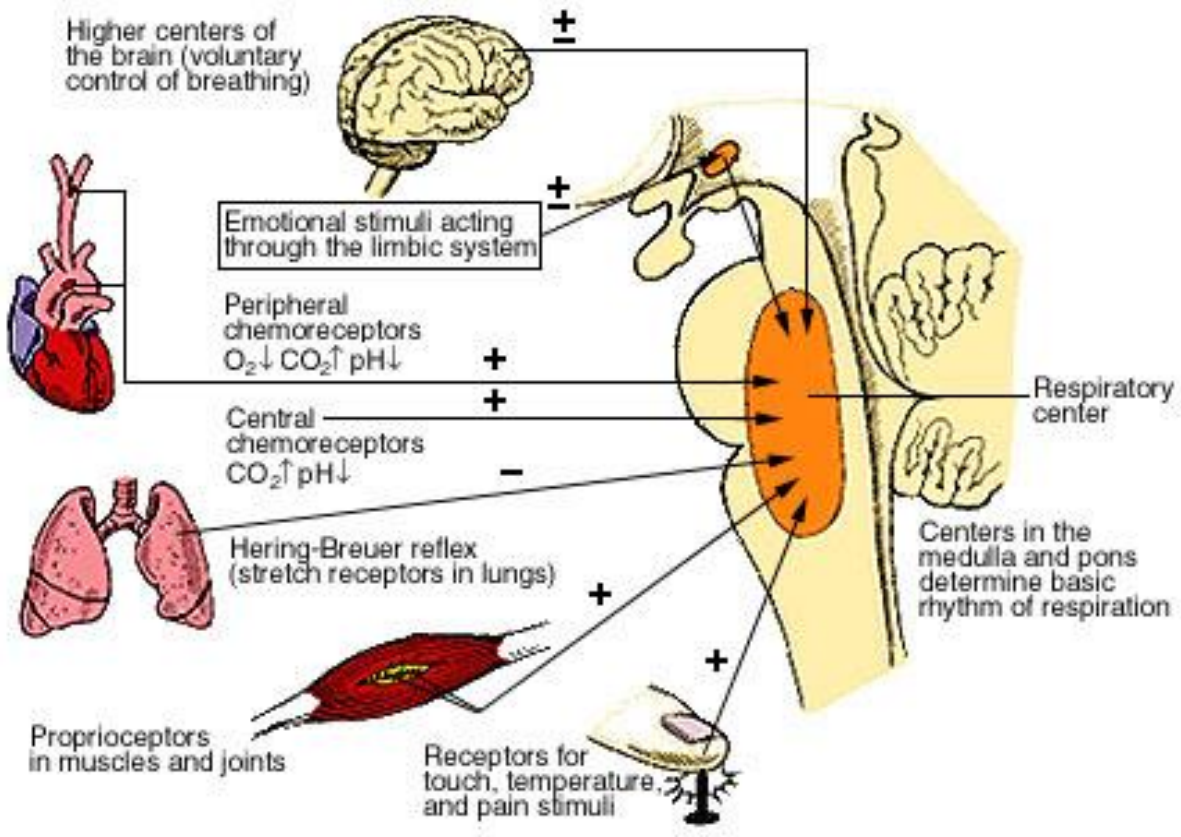
- differences in the stimulation of respiration by pCO_2 ($[H^+]$ resp. in the CSF) and/or pO_2<60mmHg
- changes of alveolar ventilation
- disorders:
  - acidemia
    - → respiratory centre of the brain
    - → ↑alveolar ventilation
    - → ↓CO_2
  - alkalemia
    - → respiratory centre of the brain
    - → ↓ alveolar ventilation
    - → ↑ CO_2

$pa_{CO_2} = V_{CO_2} / V_a$



Total CO_2 carried by blood:
= $[HCO_3]$ + $[H_2CO_3]$
+ [carbamino CO_2]
+ [dissolved CO_2]

Respiratory centre

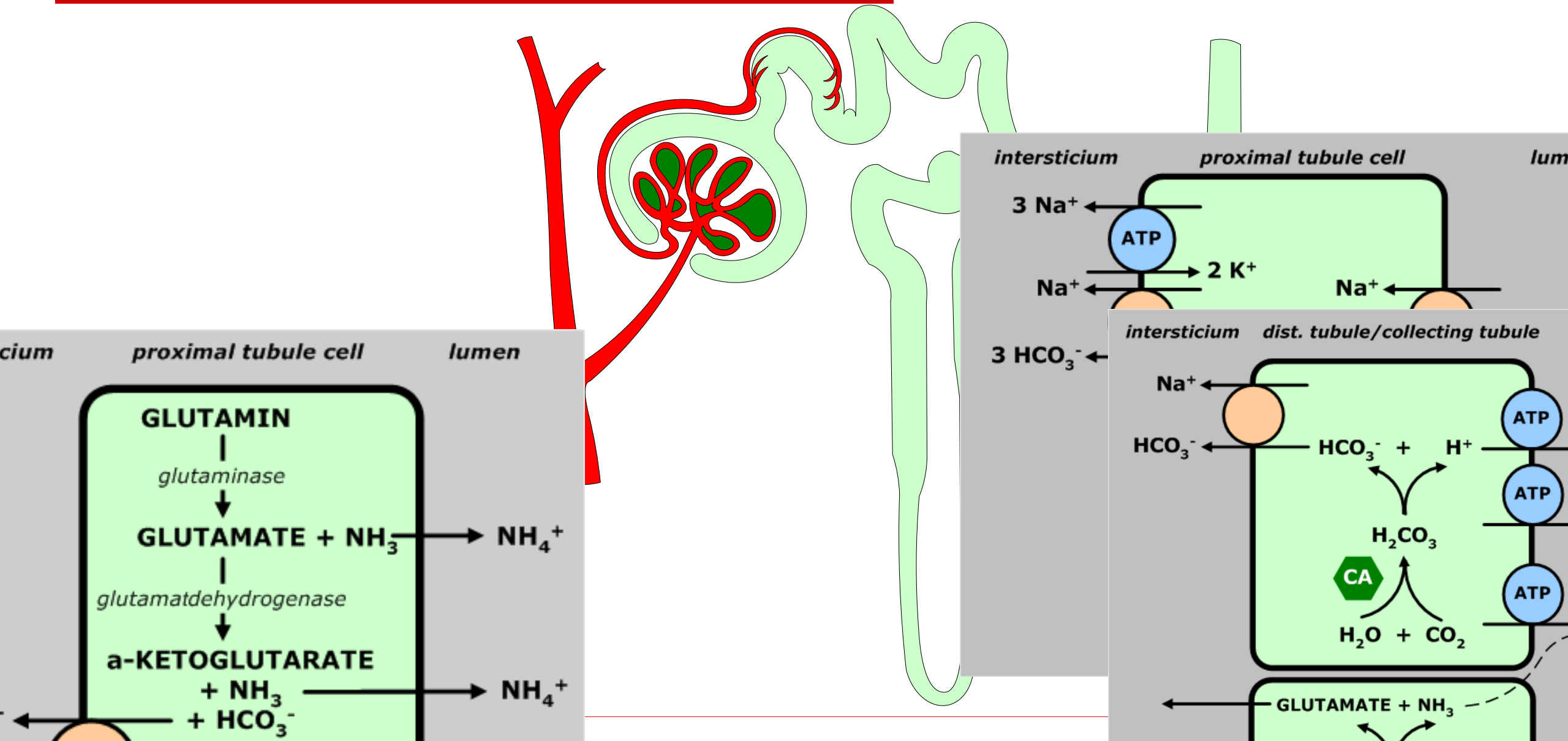


- long-lasting respiratory acidosis (↑ $PaCO_2$) decreases sensitivity of resp. centre to $PaCO_2$ and PaO_2 becomes the main regulator
- administration of oxygen therapeutically can sometimes lead to worsening of resp. acidosis or even to respiratory arrest !!!

Renal system – fixed H^+ & HCO_3^-

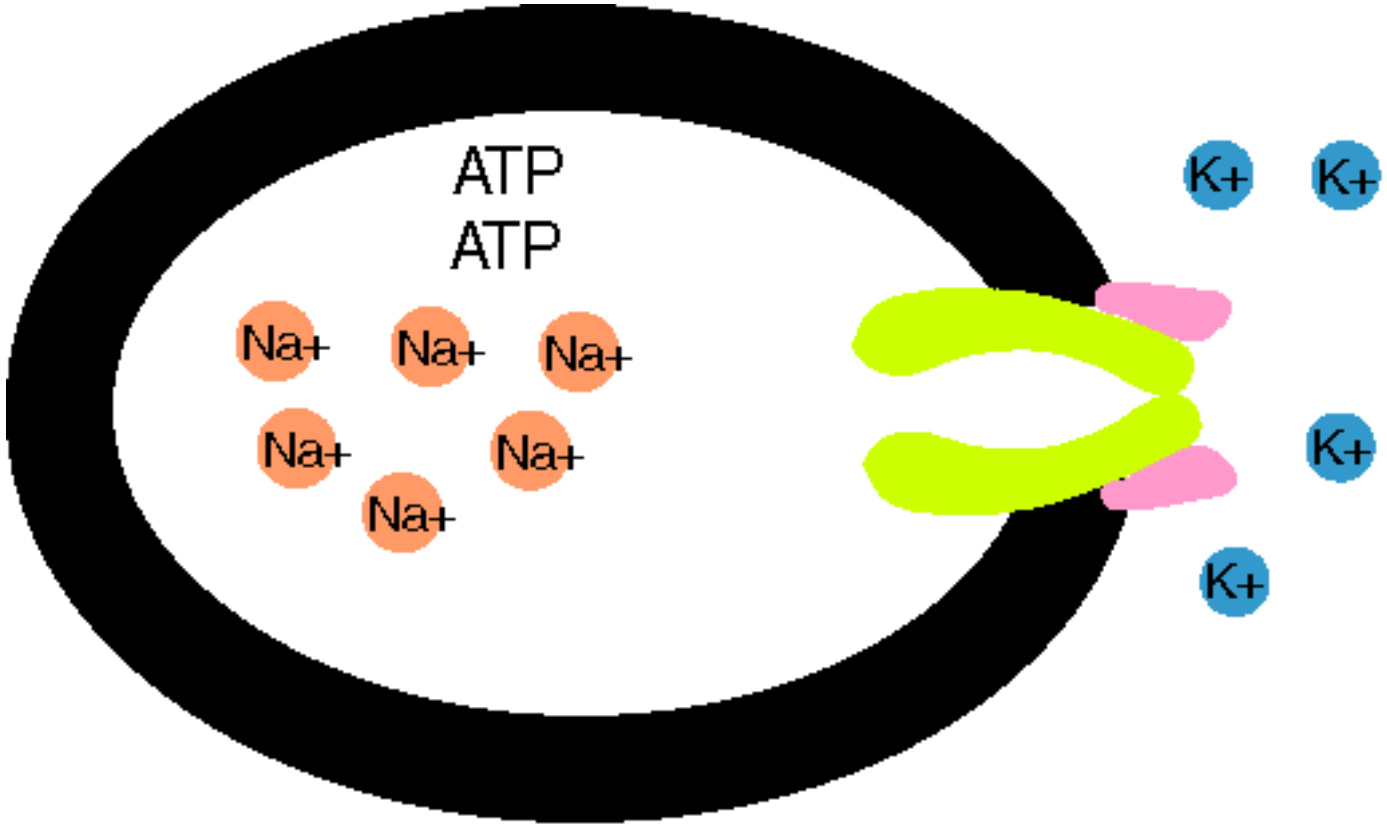
- Proximal tubular mechanisms:
  - reabsorption of **HCO_3^-** filtered at the glomerulus
    - carboanhydrase
    - NHE-3 exchanger (reabsorption of HCO_3^- is coupled with reabsorption of Na^+)
  - production of **NH_4^+**
    - from glutamine in prox. tubule with parallel formation of HCO_3^-
      - ☛ glutamine is a way of body to dispose of nitrogen (in liver)
    - most of NH_4^+ recycles in the renal medulla
- Distal tubular mechanisms:
  - net excretion of H^+
    - normally 70mmol/day
    - max. 700mmol/day
      - ☛ together with proximal tubule excretion of H^+ could increase up to 1000x!!! (↓pH of urine down to 4.5)
  - reaction with HPO_4^{2-} - formation of "titratable acidity" (TA)
  - addition of **NH_4^+** to luminal fluid
  - reabsorption of remaining **HCO_3^-**

Regulation of ABB in different parts of nephron



Na^+/K^+ ATP-ase

- electrogenic (ratio 3 Na^+:2 K^+)
- energy for secondary-active transports with Na^+



Assessment of A-B balance

	Arterial blood (interval)		**Venous blood**
pH	7.40	7.38 - 7.42	7.33 - 7.43
H^+ (nmol/l)	40	36 – 44	
pCO_2 (mmHg/kPa)	40 / 5.3	35 – 45 / 5.1 – 5.5	41 – 51
HCO_3^- (mmol/l)	25	22 - 26	24 - 28
BE	±2		
AG (mEq/l)	12	10 - 14	
Hb saturation (%)	95	80 – 95	70 – 75
pO_2 (mmHg)	95	80 – 95	35 – 49

Disorders of A-B balance

- **Acidosis vs. alkalosis:** abnormal condition lowering or raising arterial pH
  - before activation of compensatory changes in response to the primary aetiological factor
- **Simple vs. mixed A-B disorders:** single vs. multiple aetiological factors
- Disorders are defined according to their effect on pH of ECF

Acidaemia: arterial pH<7.36 (i.e. [H+]>44 nM)
Alkalaemia: arterial pH>7.44 (i.e. [H+]<36 nM)

- Primary cause → buffers → compensation → correction

Causes

- Respiratory
  - abnormal processes which tend to alter pH because of a primary change in **pCO_2** levels
    - acidosis
    - alkalosis
  - buffering
    - predominantly intracellular proteins
  - compensation
    - hyperventilation
      - ☛ typically limited, hypoventlation is often a cause of disorder
    - renal
      - ☛ delayed (days)
- Metabolic
  - abnormal processes which tend to alter pH because of a primary change in **$[HCO_3^-]$**
    - acidosis
    - alkalosis
  - buffering
    - predominantly bicarbonate system
  - compensation
    - hyperventilation
      - ☛ rapid (min - hrs)
    - renal
      - ☛ delayed (days)

Respiratory acidosis (RAC)

- primary disorder is a **↓pH** due to **↑$PaCO_2$** (>40 mmHg), i.e. hypercapnia
- time course:
  - acute (↓pH)
  - chronic (↓pH or normalisation of pH)
    - renal compensation – retention of HCO_3^-, 3-4 days

$paCO_2 = VCO_2 / VA$

- causes of RAC:
  - decreased alveolar ventilation (most cases)
    - the defect leading to this can occur at any level in the respiratory control mechanism
    - the degree of hypoxemia corresponds with degree of alveolar hypoventilation
      - ☛ enrichment of $\%O_2$ in inhaled air corrects solely "pure hypoventilation" !!!
  - presence of excess CO_2 in the inspired gas
    - re-breathing of CO_2-containing expired gas
    - addition of CO_2 to inspired gas
    - insufflation of CO_2 into body cavity (e.g. for laparoscopic surgery)
  - increased production of CO_2 by the body
    - malignant hyperthermia, sepsis

A rise in arterial pCO_2 is such a potent stimulus to ventilation that RAC will rapidly correct unless some abnormal factor is maintaining the hypoventilation

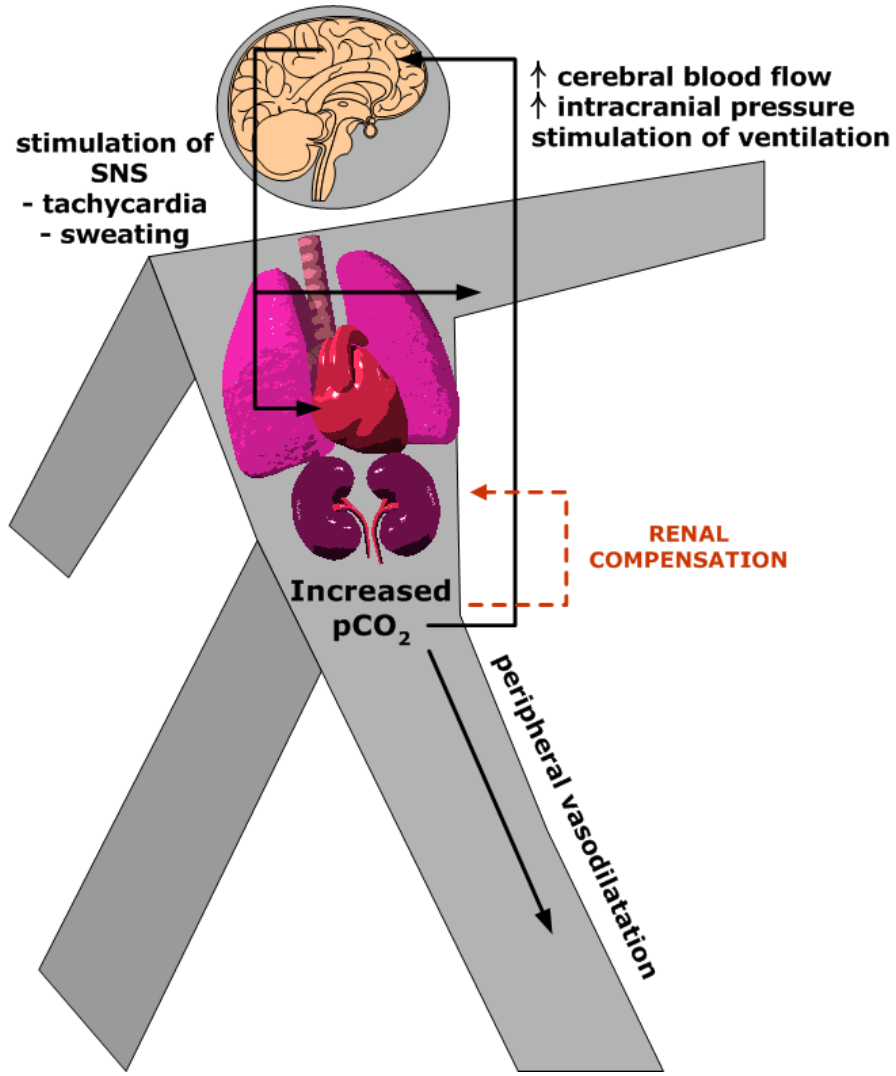
RA - inadequate alveolar ventilation

- Central respiratory depression & other CNS problems
  - drug depression of respiratory centre (e.g. by opiates, sedatives, anaesthetics)
  - CNS trauma, infarct, haemorrhage or tumour
  - hypoventilation of obesity (e.g. Pickwick syndrome)
  - cervical cord trauma or lesions (at or above C4 level)
  - high central neural blockade
  - poliomyelitis
  - tetanus
  - cardiac arrest with cerebral hypoxia
- Nerve or muscle disorders
  - Guillain-Barre syndrome
  - Myasthenia gravis
  - muscle relaxant drugs
  - toxins e.g. organophosphates, snake venom
  - various myopathies
- Lung or chest wall defects
  - acute on COPD
  - chest trauma -contusion, haemothorax
  - pneumothorax
  - diaphragmatic paralysis
  - pulmonary oedema
  - adult respiratory distress syndrome
  - restrictive lung disease
  - aspiration
- Airway disorders
  - upper airway obstruction
  - laryngospasm
  - bronchospasm / asthma
- External factors
  - Inadequate mechanical ventilation

Pathologic effects of hypercapnia

- CO_2 rapidly diffuses across membranes
  - depression of intracellular metabolism
- Extreme hypercapnia
  - cerebral anaesthetic effects (pCO_2>100mmHg)
- Effect of hypoxemia

An arterial **pCO_2>90 mmHg** is not compatible with life in patients breathing room air:
pAO_2 = [0.21x(760-47)]-90/0.8 = **37 mmHg**



RAC – compensation and correction

- Acute RAC - buffering only!
  - about 99% of this buffering occurs intracellularly
    - proteins (haemoglobin and phosphates) are the most important intravascular buffers for CO_2 but their concentration is low relative to the amount of carbon dioxide requiring buffering
  - the bicarbonate system is not responsible for any buffering of a respiratory acid-base disorder
    - the system cannot buffer itself
  - **efficiency of compensatory hyperventilation is usually limited**
- Chronic RAC - renal compensation
  - bicarbonate retention
    - takes 3 or 4 days to reach its maximum
  - ↑$paCO_2$ → ↑pCO_2 in proximal tubular cells → ↑H+ secretion into the lumen:
    - ↑ HCO_3 production which crosses the basolateral membrane and enters the circulation (so plasma [HCO_3] increases)
    - ↑ Na^+ reabsorption in exchange for H^+
    - ↑ NH_4 production and secretion to 'buffer' the H^+ in the tubular lumen, parallel regeneration of HCO_3^-
- RAC treatment
  - the pCO_2 rapidly returns to normal with restoration of adequate alveolar ventilation
    - ☛ treatment needs to be directed to correction of the primary cause if this is possible
  - rapid fall in pCO_2 (especially if the RA has been present for some time) can result in:
    - severe hypotension
    - "post hypercapnic alkalosis"

Respiratory alkalosis (RAL)

- causes: respiratory alkalosis is ALWAYS due to increased **alveolar** ventilation (hyperventilation)
  - low arterial pCO_2 will be sensed by the central chemoreceptors and the hyperventilation will be inhibited unless the patient's ventilation is controlled
- (1) central causes (direct action via respiratory centre)
  - head injury
  - stroke
  - anxiety-hyperventilation syndrome (psychogenic)
  - other 'supra-tentorial' causes (pain, fear, stress, voluntary)
  - various drugs (e.g. analeptics, propanidid, salicylate intoxication)
  - various endogenous compounds
    - toxins in patients with chronic liver disease
    - progesterone during pregnancy
    - cytokines during sepsis
- (2) hypoxaemia (act via peripheral chemoreceptors)
  - respiratory stimulation via peripheral chemoreceptors
- (3) pulmonary causes (act via intrapulmonary receptors)
  - decreases pulmonary compliance
    - pulmonary embolism
    - pneumonia
    - asthma
    - pulmonary oedema (all types)
- (4) iatrogenic
  - excessive controlled ventilation

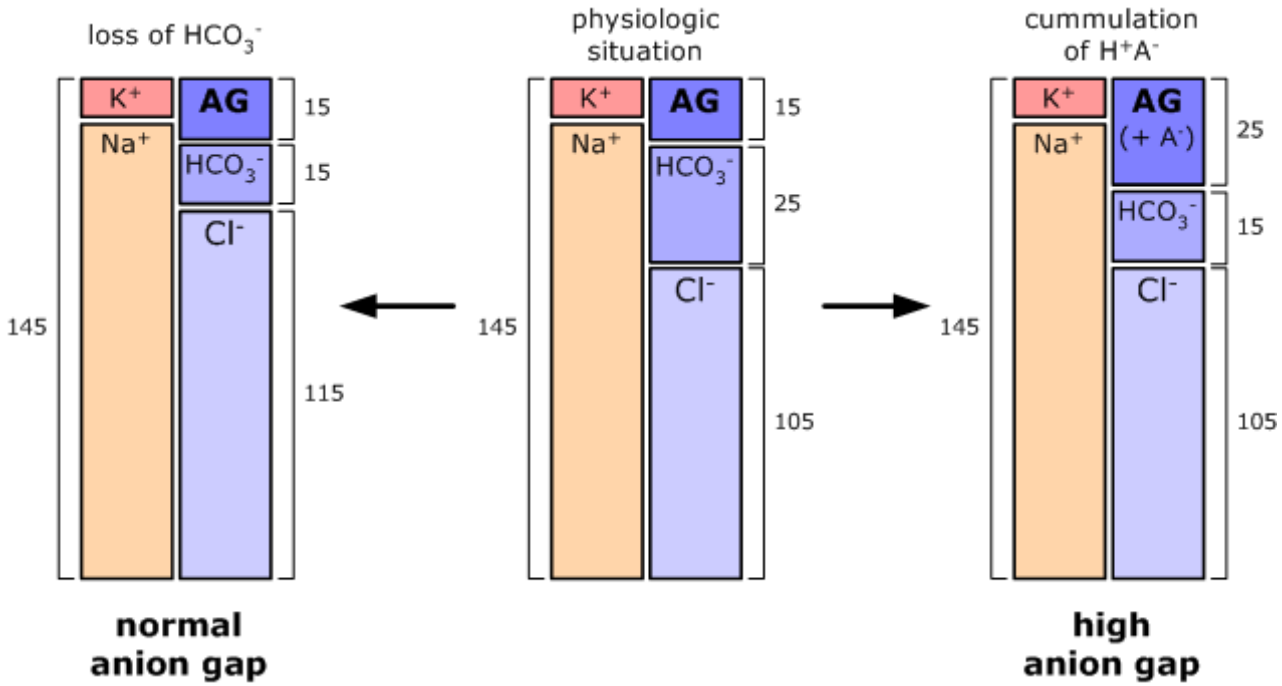
decrease in pCO_2 that occurs as a compensation for metabolic acidosis is not a respiratory alkalosis as it is not a primary process = **hypocapnia is not synonymous with respiratory alkalosis** !!!

Metabolic acidosis (MAC)

- Primary disorder is a **↓pH** due to **↓HCO_3^-**

- Pathophysiology:
  - ↑ fixed $[H^+]$ = **high anion gap (AG)**
  - loss or ↓ reabsorption of HCO_3^- = **normal AG**

$$AG = [Na^+] + [K^+] - [Cl^-] - [HCO_3^-]$$

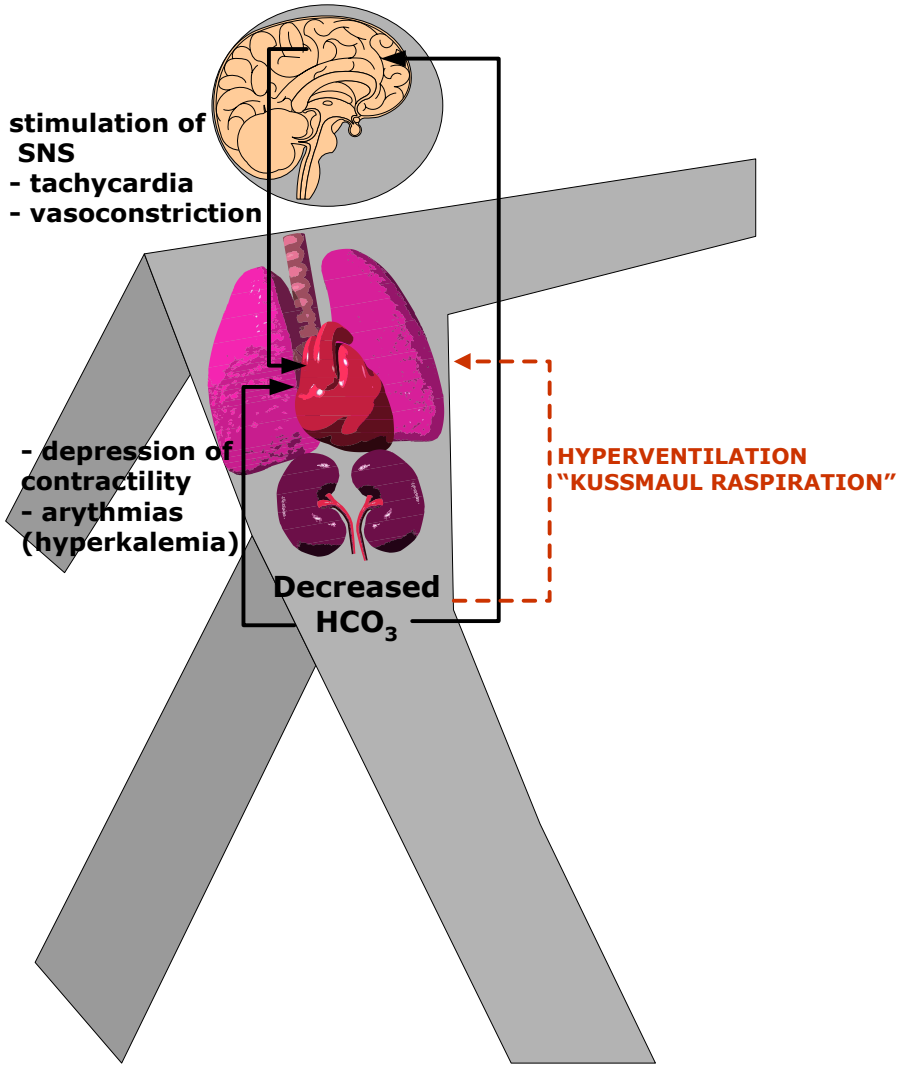


Aetiology of MAC

- High AG
  - ketoacidosis
    - diabetic
    - alcoholism
    - starvation
  - lactic acidosis
    - type A – hypoxia/hypo-perfusion
    - type B – therapy (diabetes – biguanids)
  - renal failure
    - acute
    - chronic = uremia
  - intoxication
    - ethylenglycol
    - methanol
    - salycilates
- Normal AG (hyperchloremic)
  - renal
    - renal tubular acidosis
  - GIT
    - diarrhoea
    - enterostomy
    - drainage of pancreatic juice or bile
    - intestinal fistula

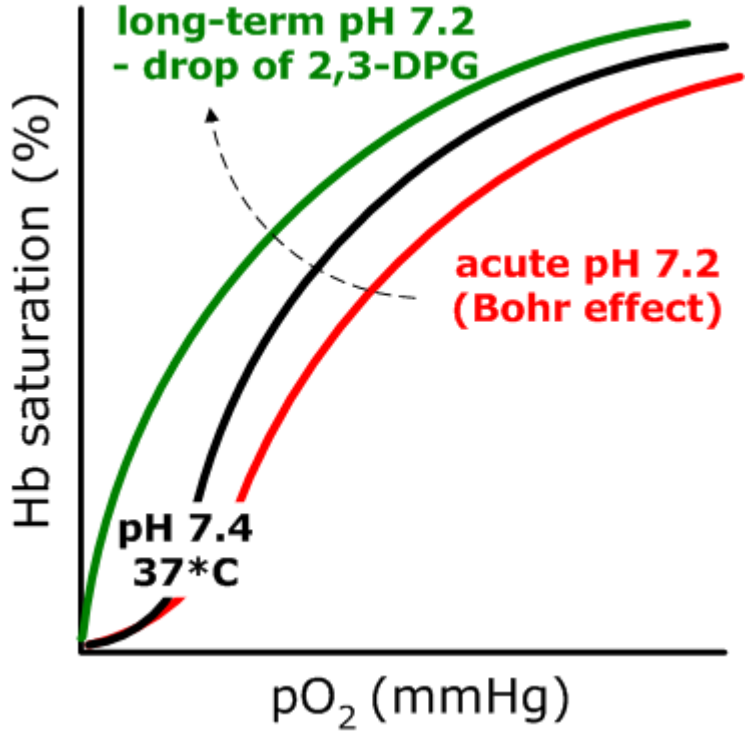
Pathologic effects of MAC

- Respiratory
  - hyperventilation
  - shift of haemoglobin dissociation curve to the right
- Cardiovascular
- Others
  - increased bone resorption (chronic acidosis only)
  - shift of K^+ out of cells causing hyperkalemia



Some effects of MAC are opposite

- Cardiovascular system
  - pH>7.2 - effect of SNS stimulation dominates (catecholamines)
  - pH<7.2
    - direct inhibitory effect of $[H^+]$ on contractility
    - vasodilatory effect of $[H^+]$
- Hb dissociation curve
- Plasma $[K^+]$ reflects
  - K^+/H^+ exchange
  - glomerular filtration rate
    - e.g. renal failure
  - osmotic diuresis
    - e.g. ketoacidosis



Common types of MAC - ketoacidosis

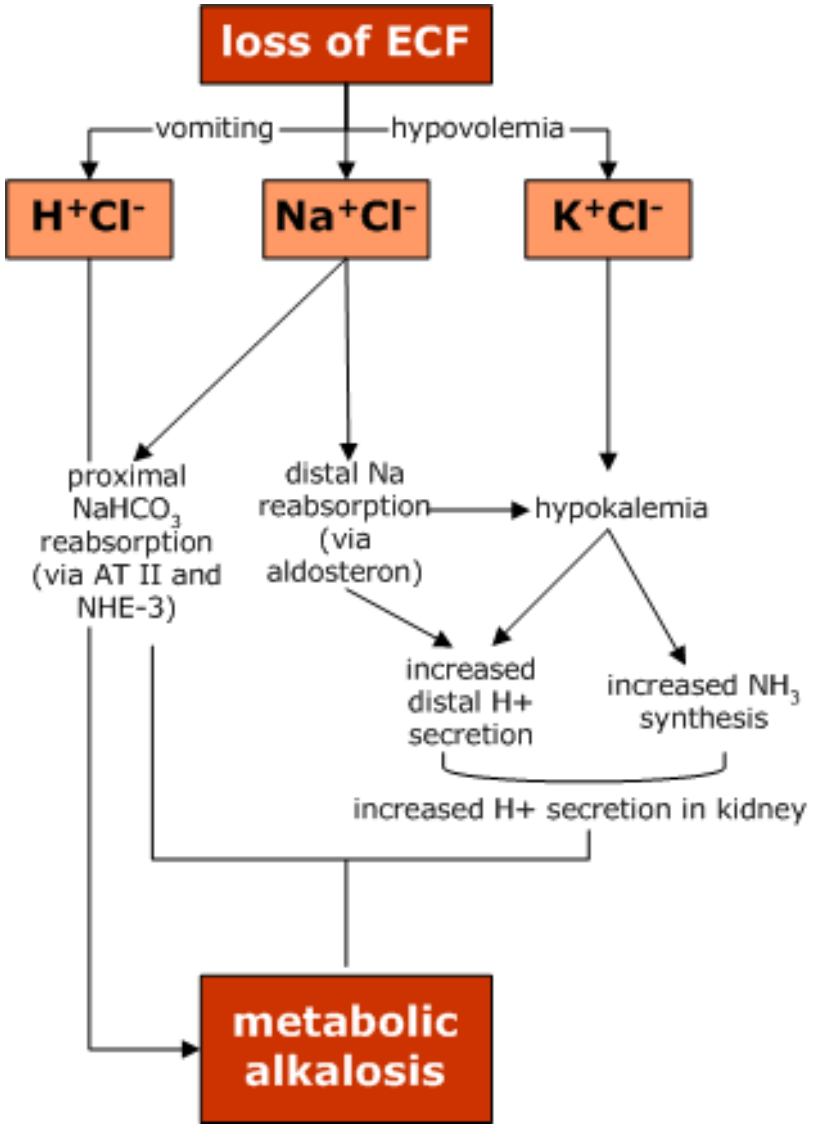
- Contributing disorders
  - increased lipolysis in adipose tissue – mobilisation of NEFA
  - increased production of keton bodies from acetyl CoA (lipolysis of TG) in liver (β-hydroxybutyrate, acetoacetate, acetone)
    - their mutual ratio depends on ration $NADH/NAD^+$
- Ketoacidosis is a consequence of
  - ↓ insulin/glucagon
  - ↑ catecholamines, ↑ glucocorticoids
- (1) Diabetic
  - hyperglycaemia + precipitating factors (stress, infection)
    - lipolysis (insulin, catecholamines) – NEFA – dysregulation of NEFA metabolism in liver (insulin, glucagon) – ↑NEFA oxidation -↑acetyl CoA – ketogenesis
  - clin. manifestation results from hyperglycaemia and ketoacidosis
- (2) Alcoholic
  - typically chron. alcoholic several days after last binge, starving
    - ☛ metabolism of ethanol to acetaldehyde and acetate consumes NAD^+
    - ☛ inhibition of gluconeogenesis favouring ketogenesis
- (3) Starvation

Common types of MAC - lactic acidosis

- Under normal circumstances entire lactate recycles
  - lactate - pyruvate - complete oxidation
  - gluconeogenesis (60% liver, 30% kidney)
  - renal threshold (5 M/L) guarantees a complete reabsorption under the normal circumstances
- Lactic acidosis
  - increased production
    - physical exercise, convulsions
      - ☛ hepatic metabolism effective enough to prevent prolonged acidosis
  - impaired metabolism of lactate
    - type A = hypoxic
      - ☛ shock (hypovolemic, distributive, cardiogennic), hypotension, anemia, heart failure, liver failure, malignancy, … most often in combination !!!
    - type B = inhibition of complete metabolism of lactate
      - ☛ drugs – biguanids (inhibition of ox. phosphorylation in mitochondria)

Metabolic alkalosis (MAL)

- ↑**pH** due to ↑**HCO_3^-**
- Pathophysiology (according to the event. parallel change of circulating volume):
  - (A) hypovolemic MAL - compensatory retention of Na kidney (aldosteron) leads to an increased excretion of H^+
    - loss of acidic ECF –prolonged vomiting or gastric juice drainage
    - overuse of diuretic (apart from acetazolamide and K-sparing diuretics)
    - congenit. hypochloremia
    - some diarrhoeas (secretory type – Cl losses)
    - diabetes insipidus
    - Barter's syndrome
  - (B) normo-/hypervolemic MAL
    - posthypercapnic
    - increased alkali intake (antacids - $NaHCO_3$, $CaCO_3$)
    - primary hyperaldosteronism
    - secondarr hyperaldosteronism (e.g. renovascular hypertension)
    - Cushing syndrome
    - liver failure (tertiary hyperaldosteronism)
      - ☛ combined with RAL due to stimulation of resp. centea by liver toxic metabolites
- compensation
  - buffers
  - retention of pCO_2 by ↓ stimulation of resp. centre
    - however limited - ~ pCO_2= 55mmHg hypoxia becomes regulatory parameter
  - renal compensation limited as well because kidney either pathogenetically contributes to MAL (B) or counteracts hypovolémia (A) – circulus vitiosus




FFFFT!
CARBON DIOXIDE EMISSION CONTROL AUTHORITY
'SUPER-STICK' MASKING TAPE