# General Physiology

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Cell Membrane

- Made of
  - Phospholipids
  - Proteins
  - Cholesterol - Found in eukaryocytes i.e., cells with nuclei
- Cell membrane = 7.5 nm thick semi-permeable structure

Lipid Bilayer

- Fluid rather than solid
- Phospholipids have:
  - eg. phosphatidylcholine & phosphatidylethanolamine
  - Hydrophilic head
    - Water soluble
    - Exposed to aqueous exterior & interior
  - Glycerol backbone
  - Fatty acid tails
    - Hydrophobic
    - Meet in middle of cell membrane
- Proteins can be either:
  - Integral – i.e., pass through bilayer eg ion channels
  - Peripheral = straddling
    - Make up 50% of cell membranes mass

Function of CM Proteins

1. Structural
2. Carriers for facilitated diffusion (i.e., down electrochemical gradient)
3. Pumps for ion active transport
4. Ion channels (diffusion down electro- or chemical gradient or both; eg K-“leak” channels)
5. Receptors for chemical messengers (i.e., hormones, neurotransmitters, autacoids…)
6. Enzymes
7. Glycoproteins involved in AB processing or anticoagulation (e.g., the mucopolysaccharide glycocalyx of the endothelium which repels clotting factors + PLT’s → helps prevent blood from clotting in intact blood vessels)

Underlying CM

- Basement membrane or basal lamina
- Made up of:
- Collagens
- Laminins
- Fibronectins
- Proteoglycans

- Function to bind cells & regulate development & growth

**Intercellular Connections**

- 2 main types:
  - adhesive type connections
  - transfer type connections

**Adhesive type Connections**

- tight junctions:
  - aka zona occludens
  - attachments between cell membrane at apical margins
  - differ in leakiness:
    - tight = impermeable eg distal renal tubule for water, BBB, bladder
    - leaky = paracellular permeable eg prox renal tubule, small intestine, liver
  - help maintain cell polarity & prevent movement of proteins in plane of CM (is a protein inserted into apical CM will stay there)

- zonula adherens:
  - lies below tight junction ie almost a continuous structure
  - contains cadherins
  - acts as site for attachments of cellular microfilaments

- desmosomes:
  - patches of apposed thickenings of membranes of adjacent cells

- hemidesmosomes:
  - attach cells to underlying basal lamina
  - attached intracellular to filaments
  - contain integrins (not cadherins)

- focal adhesions:
  - also attach to basal laminae
  - labile
  - associated with actin filaments inside cell
  - have role in cell movement

**Transfer Type Connections**

- GAP junctions:
  - Six subunit protein connections
  - Between cells which are apposed
  - Form low electrical resistance channels
  - Permit intercellular communication (eg current flow & electrical coupling between myocardial cells via ions, aa, sugars)
  - @GAP junction Intercellular space narrows from 25 ⇒ 3nm
  - diameter of junctions regulated by:
    - pH
    - voltage
    - Intracellular calcium
Transport Across Cell Membranes

- Water, ions, substances can cross cell membrane by:
  - Bulk flow:
    - Aka ultrafiltration
    - Eg fluid movement between capillaries & interstitium 2nd to Starlings forces
    - If bulk flow of solvent then also drags some solute
      \[ \leftrightarrow = \text{solute drag} \]
  - Exocytosis & endocytosis
  - Diffusion:
    - Down gradients through:
      - Directly through membrane
      - Through protein channels:
        - Voltage
        - Ligand gated
  - Carrier mediated diffusion
    - Where protein binds & carries
    - Facilitated diffusion = when item moved along their gradient (chem or electrical) no energy is needed eg GLUT transporters
  - Active transport
    - Primary –
      - Hydrolysis of ATP
      - Uniports = transport 1 substance
      - Symports = need to bind more than 1 substance for movement to occur
      - Antiports = exchange one for another
    - Secondary active
      - Counter-transport

Exocytosis/Endocytosis

Exocytosis
- Vesicle containing material sent to cell membrane
- Fusion with CM
- Ca dependant exocytosis
- 2 pathways:
  - Nonconstitutive pathway =
    - Aka regulated pathway
    - Protein from Golgi enter secretory granules
    - Process of prohormones to hormones occurs before exocytosis
  - Constitutive pathway =
    - Prompt transport of proteins to cell membrane in vesicles with no processing

Endocytosis
- Reverse of exocytosis
- Different methods:
  - Phagocytosis =
    - Cell eating
    - Material makes contact with CM which then invaginated
    - Invagination pinched off \( \Rightarrow \) engulfed material in vacuole with intact CM
  - Pinocytosis =
    - Cell drinking
    - Vesicles much smaller
    - Substance ingested in solution
  - Clathrin mediated endocytosis =
- where protein clathrin accumulates in CM
- clathrin forms a geometric array that surrounds endocytotic vesicle
- GTP binding protein dynamin involved at neck
- When vesicle formed clathrin falls off & is recycled
- Responsible for internalisation of many receptors & ligands bound to them eg LDL, nerve growth factor
  - Caveolae =
    - Areas rich in cholesterol & sphingolipids
    - Caveolin found in CM (similar to clathrin)
    - Dynamin also involved
  - Nonclathrin/noncaveolar endocytosis

**Diffusion**
- Usually down chemical =/- electrical gradient ie no energy needed
- Summarized by Fick’s equation

\[
J = -D \cdot A \cdot \frac{(\Delta c)}{x}
\]

\(J\) = net rate of diffusion
\(D\) = diff coefficient and is \(- \text{sol} / \sqrt{\text{mw}}\) (Graham’s Law)
\(A\) = area
\(c\) = concentration
\(x\) = thickness of membrane

**Osmosis**
- = diffusion of solvent molecules into a region with higher conc of a solute to which the membrane is impermeable
- osmotic pressure = pressure necessary to prevent solvent migration into its compartment
- osmotic pressure =

\[
p = \frac{n \cdot R \cdot T}{V}
\]

\(p\) = osmotic pressure
\(n\) = number of particles
\(R\) = gas constant
\(T\) = temp
\(V\) = volume

\(\therefore\) if \(T\) held constant: \(p \propto\) number of particles/unit of volume

**Gibbs-Donnan Effect**
- definition:
  - semipermeable membrane separates 2 solutions
  - 1 solution contains non diffusible charged species
  - THEN the distribution of all other diffusible univalent cations & anions across the membrane is altered in predictable manner ie at equilibrium the conc ratios are equal
- More complex for divalent ions due to protein binding
- NET effect:
  - On side of non-diffusible ion = more ions
  - \(\therefore\) if situation is intracellular \(\Rightarrow\) osmotic movement of water into cell \(\Rightarrow\) cell rupture
  - \(\therefore\) eg -ve change intracellular protein
  - this process opposed by Na/K/ATPase

**importance of Gibbs-Donnan effect**
- maintain & stabilise cell volume:
  - balance of:
• intracellular: non diffusible proteins & inorganic phosphates
• ECF: non diffusible Na – due to Na/K/ATPase pumping it out & low membrane permeability
  o = Double Donnan effect
  o if Na/k/ATPase stops working ⇒ influx of Na & water ⇒ cell rupture
• contribution to plasma oncotic pressure:
  o equilibrium ⇒ alteration distribution of other ions across CM
  o ⇒ small NET ↑ in ions in plasma
  o ⇒ ↑↑plasma oncotic pressure in capillary blood ie 15 to 25mmHg
• contributes to resting membrane potential:
  o small effect
  o small amount of:
    • intracell: ↑cations
    • ECF: ↑anions

Ion Channels
• Channels exist
  o specific for K+, Na+, Ca+, Cl-
  o non specific cations & anions

Na/K/ATPase
• Na-K Pump
  • enzyme which catalyses the hydrolyses of ATP ⇒ ADP
  • heterodimer made of:
    o α subunit =
      • MW ~ 100K
      • Transport of Na/K
• Spans cell membrane x10
• Amino-carboxyl terminals intracellular
  o β subunit =
    • MW ~55K
    • Glycoprotein
• Movement of Na & K major energy process of body:
  o Cells – 24% energy used
  o Neurons – 70% energy used
• both subunits extend thru CM
• separation of subunits kills pump
• when Na binds to α subunit ⇒ ATP also binds and converted to ADP
• energy used to extrude 3 Na, and move 2 K into cell or each ATP
• actively inhibited by ouabain
  ℭ related to digitalis glycosides
• found in all parts of body

Functions
• functions include:
  o genesis & maintainence of RMP
  o stability of cell volume
  o transport of substances across membranes (primary & secondary active)
  o hydrogen in secretion in kindey
  o signal transduction

Regulation
• ↑intracellular Na
• 2nd messengers produced in cells eg cAMP, DAG, arachidonic acid derivates
• thyroid hormones ⇒ ↑activity & ↑number of Na/K pumps
• aldosterone ⇒ ↑number of pumps
• dopamine – inhibits pump in kidneys ⇒ natriresis
• insulin ⇒ ↑activity

Secondary Active Transport
• = active transport of Na coupled to transport of other substances
• eg Na/K/ATPase creates an elec-chem gradient by pumping Na out of cells into ECF:
  o eg mucosal cells of small intestine: symport which transports glucose only if Na also attached
    and moves at same time
  o myocardium- NCX pump

Organelles

Mitochondria
• mitochondria have own genome & ability to manufacture own RNA & proteins
• their ribosomes = 70S type (30S & 50S) ie same as bacteria
  ℭ rest of cell has 80S ribosomes
Structure
• 1-10um
• outer membrane:
  o encloses whole organelle
  o contains several integral proteins = porins
  o porins form large aqueous channels which allow passage of movement of molecules up to 5000D
• intermembrane space:
  o between outer & inner membrane
  o chemically equivalent to cells cytosol
  o contains cytochrome-c
• inner membrane:
  o no porins
  o controlled permeability via transporter proteins
  o proteins have diff functions:
    ▪ proteins carrying out oxidative reactions of resp chain
    ▪ ATP synthase – makes ATP in matrix
    ▪ Transport proteins
    ▪ Protein import machinery
• Cristae:
  o Formed by folded inner membrane
  o Vastly ↑s surface area for ATP production
  o Cells which more active eg mm have more cristae
• Matrix:
  o Space enclosed by inner membrane
  o Impt in ATP production
  o Contains highly conc mixture of
    ▪ hundreds of enzymes
    ▪ mitochon ribosomes (70S)
    ▪ tRNA
    ▪ several copies of DNA genome
  o major function of enzymes =
    ▪ oxidation of pyruvate & Fas
    ▪ citric acid cycle

Function
• main = ATP production which needed for cellular metabolism
• other functions:
  o cell signalling
  o apoptosis
- cellular differentiation
- cell growth

**Oxidative Phosphorylation - Mitochondria Energy Production**
- Mitochondria found in high concentration in cells with high metabolic demands, e.g., myocardium (23% of cells), brown fat (neonate)
- Exercise ↑s numbers
- OP = production of ATP associated with oxidation by the flavoprotein cytochrome system in mitochondria

**ATP formed in electron transfer chain:**
- Substrate diffuses into mitochondria cytoplasm
- Hydrogen removed by a dehydrogenase
- NAD carries hydrogen to respiratory chain
- Hydrogen ionises and protons pass along series of carrier molecules across an insulating membrane (inner membrane of mitochondria – forms cristae)
- Movement of protons creates an electrochemical gradient for transport of protons from intermediate space back into matrix ⇒ this drives a reversible ATPase in the inner membrane (ATP synthase)
- ATP synthase: ADP + Pi → ATP
- O2 required to oxidise NADH

Reduction of O2 to water – catalysed by cytochrome oxidase

cyanide inhibits this oxidase ∴ inhibits OP in mitochondria
• Eg’s of carrier molecules in electron transfer chain
  o Flavoprotein
  o Cytochromes A, A3, B, C, C1
  o Ubiquinone
  o Several iron sulphide proteins

• OP depends on:
  o Adequate supply of ADP +ve feedback loop eg ↑ATP utilisation ⇒ ↑ADP ⇒ ↑OP
  o Rate of delivery of fats, lactate, glucose to interior of mitochon
  o Availability of O2:
    ▪ Pasteur point = 1-2mmHg ie point below OP cannot occur
• ∴ cardioresp works in harmony to ensure O2 reaches cells
  o defined by oxygen flux equation:
    \[ \text{DO}_{2\text{body}} = \text{CaO}_2 \times \text{CO} \]

• lack of oxygen causes:
  o nothing to scavenge H+ at end of transfer chain
  o transfer chain ceases
  o build up of reduced compounds ⇒ inhibits TCA cycle ⇒ inhibition of glycolysis
  \[ \rightarrow \text{but glycolysis continues as lactate dehydrogenase removes reduced compounds} \]

Endoplasmic Reticulum
• complex system of tubules in cytoplasm
• tubule walls made of membrane
• rough ER =
  o ribosomes (granules) attaches to cytoplasmic side of membrane
  o involved in protein synthesis:
    ▪ folding polypeptide chains
    ▪ form S-S bonds
• smooth ER =
  o attached ribosome absent (but free ribosomes in cytoplasm)
  o function:
    ▪ site of steroid synthesis
    ▪ detoxification processes
• sarcoplasmic reticulum = imp't role in skeletal & cardiac mm functioning

Ribosomes
• eukaryotes =
  o 80S – 60S & 40S subunits
  o 22-32nm
  o site of protein synthesis
  o contain
    ▪ many proteins &
    ▪ at least 3 ribosomal RNAs
  o ribosomes attached to ER synthesize proteins for eg
    ▪ hormones for secretion
    ▪ proteins seregated in lysosomes
    ▪ proteins in cell membranes
  o free ribosomes in cytoplasm:
    ▪ protein in Hb
    ▪ protein in mitochondira
• Golgi apparatus involved in processing proteins found in ribosomes

Cell Receptors & Secondary Messengers within Cells
• Extra-cellular ligands = 1st messangers
• Intracellular mediators = 2nd messangers

Types of receptors:

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<th>Type3</th>
<th>Type4</th>
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<td>G-prot coupled</td>
<td>Kinase-linked</td>
<td>Nuclear</td>
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<tr>
<td>ionotropic</td>
<td>metabotropic</td>
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<tr>
<th>Location</th>
<th>Effector</th>
<th>2nd msgr</th>
<th>Coupling</th>
<th>E.g.’s</th>
<th>Time</th>
<th>Structure</th>
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<td>membrane</td>
<td>ion channel</td>
<td>c-AMP/c-GMP</td>
<td>G-prot</td>
<td>n-AchR</td>
<td>millisec’s</td>
<td>oligomeric assembly of subunits around central pore</td>
</tr>
<tr>
<td>membrane</td>
<td>Ch or enzyme</td>
<td>IP3 / DAG</td>
<td>direct</td>
<td>m-AchR</td>
<td>seconds</td>
<td>Monomer with 7 transmembrane helices</td>
</tr>
<tr>
<td>membrane</td>
<td>enzyme</td>
<td>--</td>
<td>via DNA</td>
<td>Insulin</td>
<td>hrs</td>
<td>Single trans-membr helix linking EC R domain to IC kinase domain</td>
</tr>
<tr>
<td>intracellular</td>
<td>gene transcription</td>
<td>--</td>
<td></td>
<td>steroid, thyroid H receptors</td>
<td>hrs</td>
<td>Monomeric str with separate R and DNA binding domains.</td>
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General Principles - 11
**Type 1 - Ionotropic**

- See prev notes on NaKATPase & ion channels

**Type 2: G Proteins & P Protein Coupled Receptors (GPCRs)**

- **GPCR** = monomer compromising 7 membrane spanning segments
- One of intracellular loops = larger & interacts with G protein
- ∴ GPCR couple to intracellular effector systems via a GP
  \[\text{GPCR} \rightarrow \text{G Protein 100: 1 GPCR} \text{ (amplification system)}\]
- G proteins =
  - membrane proteins coupled to specific receptors
    \(\text{GPCR} \rightarrow \text{G Protein} \)
  - non selective workhorses for GPCR they are coupled to.
    \(\text{GPCR} \rightarrow \text{G Protein} \)
- G proteins =
  - Alpha –
    - bound to GDP
    - possesses intrinsic GTPase activity
  - Beta
  - Gamma
- **Process of activation:**
  - Ligand bind to GPCR \(\Rightarrow\) GDP on alpha subunit is exchanged for GTP
  - Alpha subunit separates from combined Beta & gamma subunit
    \(\text{GPCR} \rightarrow \text{G Protein} \)
  - Alpha-GTP complex free to activate an effector eg membrane enzyme or channel
- **Activation terminated**
  - when bound GTP hydrolysed to GDP
    \(\text{GPCR} \rightarrow \text{G Protein} \)
  - intrinsic GTPase ability of alpha subunit is upregulated when bound to target protein
  - alpha (& bound GDP) then reattach with beta-gamma subunits
- 1400 combinations of alpha, beta, gamma combinations to control different effectors
- complex activation process \(\Rightarrow\) slower onset than ionotropic receptors eg GABA, n-ACH = milliseconds

**Targets of GPs**

G protein can activate:
- adenylate cyclase (AC) or Guanylate cyclase (GC) \(\Rightarrow\) c-AMP or c-GMP formation
- phospholipase C (PLC) on inner surface of CM

**c-AMP**
- cyclic adenosine 3’5’monophosphate
- cAMP = physiologically active
- c-AMP formed from ATP by adenylyl cyclase
- inactivated by conversion to 5’AMP by phosphodiesterase
  \(\text{cAMP} \rightarrow \text{cAMP} \rightarrow \text{5’AMP} \rightarrow \text{5’AMP} \)
- can be inhibited by methylxantines eg theophylline

**c-GMP**
- cyclic guanosine monophosphate
- impt in vision
- guanylate cyclases = family of enzymes which catalyse formation of cGMP

**PLC**
- catalyse hydrolysis of membrane lipid PIP2 to
- inositol phosphate (IP3) or
diacylglycerol (DAG)

- IP3 – diffuses to ER where binds to IP3 receptor
  \( \Leftarrow \) ligand gated Ca channel
- DAG – stays in cell membrane where it activates protein kinase C

Types of G Proteins

- **Gs**: \( \rightarrow \) \( \uparrow \) AC(or GC) \( \rightarrow \) \( \uparrow \) c-AMP
  eg of substances causing Gs activation:
  - ADH ,
  - adrenalin(beta receptors) ,
  - adenosine (A2) ,
  - ANP ,
  - glucagon ,
  - histamine(H2)

- **Gi**: \( \rightarrow \) \( \downarrow \) AC (or GC)\( \rightarrow \) \( \downarrow \) c-AMP
  - angiotensin (AT2) ,
  - adenosine (A1),
  - alpha-2 and
  - opioid receptors.

- **Gq**: \( \rightarrow \) \( \uparrow \) PLC \( \rightarrow \) IP3 + DAG
  eg noradrenaline (alpha1) , histamine H1 ,

- **Gt**: \( \rightarrow \) stim c-GMP phosphodiesterase in photoreceptors

- **Go**: \( \rightarrow \) involved in gating of ion ch’s , \( \uparrow \) concentration in brain

Type 3 – Kinase linked

- Eg
  - insulin like growth factor 1 (IGF-1)
  - Epigermal growth factor (EGF)
- Single membrane spanning domain
- Intracellular tyrosine kinase domains
- Ligand binds to tyrosine kinase receptor\( \Rightarrow \)
  - Dimerization of 2 similar receptors
  - \( \Rightarrow \) partial activation of intracellular tyrosine kinase domains
Type 4 – Nuclear Receptors

Intracellular Calcium as a 2\textsuperscript{nd} Messenger

- Free Ca\textsuperscript{2+} conc in cytoplasm = rest 100nmol/L
- Ca conc in ECF = 1,200,000 nmol/L
  \( \Rightarrow \) ie marked inwards conc gradient
- \( \therefore \) most of intracellular Ca stored at v high conc in ER & other organelles
- Ca can enter cell by variety of methods:
  - Down gradient
  - Ligand gated or voltage gated channels
  - Stretch channels
- Secondary messengers \( \Rightarrow \) ↑intracell Ca conc by:
  - Ca release from intracellular stores
    - IP3 –
      - major 2\textsuperscript{nd} messenger with this effect
      - IP3 receptor on ER
  - ↑ed entry Ca into cells
    - SOCCs (store-operated Ca channels)
      - Transient release Ca from internal stores \( \Rightarrow \) opening SOCC on cell membrane
      - Influx of Ca replenishes & refills ER
- Movement of Ca out of cell against conc gradient:
  - Active transport – membrane Ca ATPase
  - 2\textsuperscript{nd} Active transport –
    - NCX (3 Na in for each Ca out)
    - Driven by Na gradient
- Movement of Ca into internal stores via action SERCA pump (sarcoplasmic or endoplasmic reticulum Ca ATPase)
General Principles

Definitions

- **Osmolarity**: = no of osmoles of solute per litre of solvent:
  - altered by temp changes + vol of solute
- **Osmolality**: = no of osmoles of solute per kg of solvent:
  - independent of T changes or vol of solute
- **Tonicity**:
  - = the effective osmolality of a solution.
  - = to the sum of the [ ]’s of the solutes which have the capacity to exert osmotic force across the membrane concerned.

Intracellular Fluid (ICF) & Extracellular (ECF)

- ICF cannot be measure directly
- Derived from TBW – ECF
- TBW measured by dilution principle using Deuterium oxide (D20 = a heavy water)
- ECF measured with inulin
- TB Water = 60% of total body weight
- body water can be further subdivided via simple or complex models:
  - complex (60% broken down into)
    - ICF = 55%
    - ECF = 45% which broken down into
      - 20% interstitial
      - 7.5% intravascular
      - 7.5% bone
      - 7.5% dense CT
      - 2.5% transcellular fluid eg CSF, urine in bladder etc
  - simple (% = breakdown of 60%) (bracketed = fraction of 60%)
    - 40% ICF (2/3)
    - 20% ECF (1/3)
      - 5% plasma (1/4)
      - 15% interstitial (3/4)
- ∴ 70kg person:
  - TBW = 42litres
  - ICF = 28litres
  - ECF = 14 litres:
    - 3.5 litres plasma
    - 10.5 litres interstitial fluid
Other Body Weights
- weights:
  - 60% fluid
    - intracellular - 40%
    - extracellular - 20%
  - 17% protein
  - 15% fat
  - 7% mineral

**Control of Cell Volume**
- H20 can cross CMs freely ∴ could lead to:
  - Change ECF tonicity
  - Change in cell volume
  - but doesn’t
- Cell contain sig conc of anions which non-diffusable
  - proteins & organic phosphates
- Creates Donnan effect across CM ⇒ intracellular anions drawing water into cell ⇒ cell rupture if nt counterbalanced!
- Counterbalance =
  - Donnan effect in opposite direction set up by Na in ECF
  - Na in ECF effectively non diffusible due to Na/K/ATPase pump & ↓ed Na CM permeability
  - double Donnan effect ⇒ stable cell volume
  - reliant on Na/K/ATPase

**Changes to Tonicity**
- Acute change in ECF tonicity ⇒ acute change in cell volume
- Adaptation can occur with time:
  - Cell adapt to minimise disruption caused by change in ECF tonicity
  - Done by changing intracellular solute content
  - ie lose or gain solute to minimise volume changes
- Eg ECF hypertonicity:
  - ⇒ IC dehydration
  - cell will gain solute from ECF or ↑production of own solute

**Mole**
- = gram molecular weight of a substance
- 1mol NaCl = 23g + 35.5g = 58.5g
Water

- H₂O has a dipole moment:
  - O₂ pulls away electrons from the hydrogen atoms \( \Rightarrow \) slightly polar
  - allows water to dissolve variety of charged atom & molecules
  - allows H₂O – H₂O bonding via Hydrogen bonds

- hydrogen bond network causes:
  - high surface tension
  - high heat vaporisation & heat capacity
  - high dielectric constant

Electrolytes

- eg NaCl = molecules which dissociate in water to:
  - Na⁺ = cation
  - Cl⁻ = anion

- Tend not to reassociate in water due to elec charge

pH & Buffering

- pH = logarithm to the base 10 of the reciprocal of the H⁺ concentration
  \( \text{pH} = -\log \text{H⁺ conc} \)

- water = pH 7
- gastric acid = 2
- pancreatic enzyme = 8

- buffer = substance which has ability to bind or release H⁺ in solution thus normalising pH of solution

- isohydric principle = all buffer pairs in homogenous solution are in equilibrium with same H⁺ conc

Tonicity

- = osmolality of a solution relative to plasma
- solution which same osmolality as plasma = isotonic
- hypertonic = greater osmolality than plasma

- all solutions which initially isosmotic with plasma would remain isotonic but solutes diffuse into cells/metabolised \( \text{ie same osmotic pressure or freezing point depression} \)
  - 0.9% saline = remains isotonic – as net movement of osmotically active particles
  - 5% gluc =
    - isotonic initially
    - gluc then metabolised \( \Rightarrow \) hypotonic solution

- Na⁺, Cl⁻ & HCO₃⁻ provide most impt contribution to osmolal conc of plasma (270 of the 290mOsm/L)

Non ionic Diffusion

- Some acids/bases can cross membrane in undissociated form and not in ionic form
- \( \therefore \) move across as undisassociates and then dissociate
- = non ionic diffusion
TransMembrane Potential

Concentration of Ions

- resting cell membrane potential = -70mV

<table>
<thead>
<tr>
<th>Ion</th>
<th>Inside Cell</th>
<th>Outside Cell</th>
<th>Equilibrium Potential mV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na+</td>
<td>15</td>
<td>150</td>
<td>+60</td>
</tr>
<tr>
<td>K+</td>
<td>150</td>
<td>5.5</td>
<td>-90</td>
</tr>
<tr>
<td>Cl-</td>
<td>9</td>
<td>125</td>
<td>-70</td>
</tr>
<tr>
<td>Ca</td>
<td>100 nanomol</td>
<td>2.2-2.5 (1.15-1.3)</td>
<td></td>
</tr>
<tr>
<td>Mg</td>
<td>10 mmol</td>
<td>0.75-1 mmol</td>
<td></td>
</tr>
<tr>
<td>HCO3</td>
<td>10</td>
<td>20-30</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>7.1</td>
<td>7.4</td>
<td></td>
</tr>
</tbody>
</table>

- Na:
  - Concentration & elec gradient is inward
  - ∴ expect slow gain of intracellular Na

- K:
  - Conc gradient outward
  - Elec gradient inward
  - But conc gradient is greater ∴ expect slow outward movement

- Cl-:
  - Conc gradient inward
  - Elec gradient neutral

Genesis of Membrane Potential

- Na,K, ATPase:
  - Uses ATP to pump K back into cell
  - Keeps intracellular Na low
  - 3Na out; 2 K in ⇒ .: contributes to membrane potential
    \[\text{electrogenic pump}\]

Resting Membrane Potentials

- skeletal mm -90mV; threshold -70mV
- cardiac mm -80mV; threshold -65mV
- Neurones -70mV; threshold -55mV
- Cardiac pacemaker cells -60mV
- smooth mm – wandering baseline but average -50mV
Energy Production

- large amounts of energy released when high energy phosphate compound bonds are hydrolysed
- also see low energy phosphates
- ATP = most impt high energy phosphate:
  - ATP ⇔ ADP ⇔ AMP
  - all steps create energy

Oxidation

- Oxidation =
  - combination of a substance with O2 or
  - loss of a hydrogen or
  - loss of electrons
  - opposite = reduction
- reduction reactions:
  - NAD+ ⇔ NADP+ ⇔ NADH ⇔ NADPH
- Oxidative phosphorylation:
  - Energy from a proton gradient across mitochondrial membrane
  - Flavoprotein-cytochrome systems creates H+ movement from inner to outer lamella of mitochondria
  - Return movement of proton down proton gradient ⇔ ATP
- 90% O2 consumption in basal state = mitochondrial
  - 80% this coupled to ATP synthesis