Cellular Physiology (PHSI3009)

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- Cell membranes and communication
- 2nd messenger systems
- G-coupled protein signalling
- Calcium signalling
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- Transporter efficiency
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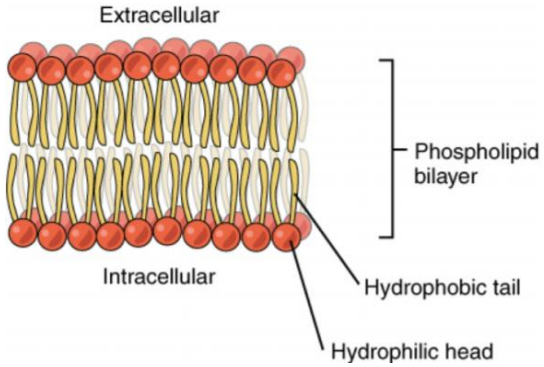
General physiology

- The study of the function of cells and the role of biomolecules that carry out these physiological functions

Cell membrane and principles of cell communication

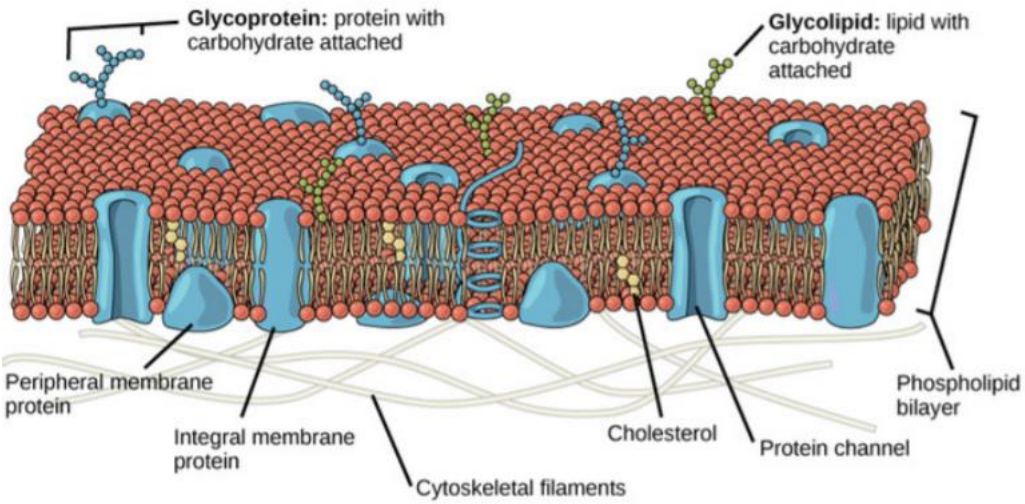
Cell membranes and compartmentalisation

- Separates the interior of a cell from the outside
- Organises the cell into functional, membrane-enclosed compartments or organelles
- **Biological reactions take place inside the membranes**
    - Membrane around lysozyme allows it to maintain acidity for reactions



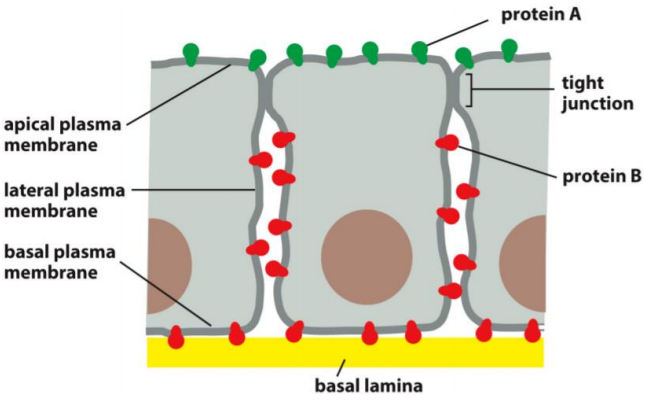
The plasma membrane:

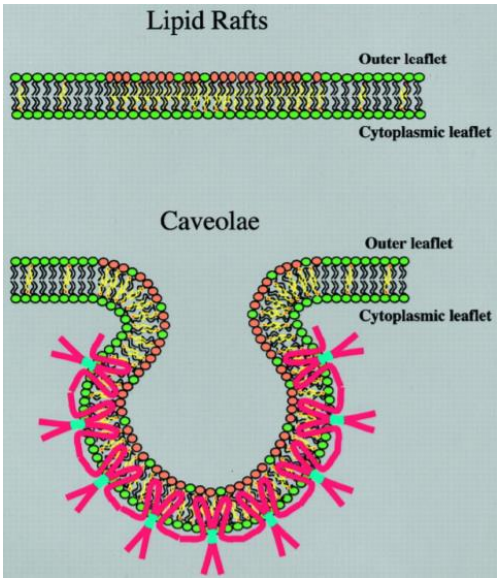
- Phospholipid bilayer
- Has **cholesterol** and **glycolipids** (lipids with carbohydrates added)
    - Changes fluidity
- Contains 500-2000 lipid species
- Liquid compositions of inner and outer membranes are different
- **Fluid mosaic model**
    - Proteins can move in lateral direction
    - Movement is dependent on interaction with cytoskeletons and extracellular matrices



Membrane proteins:

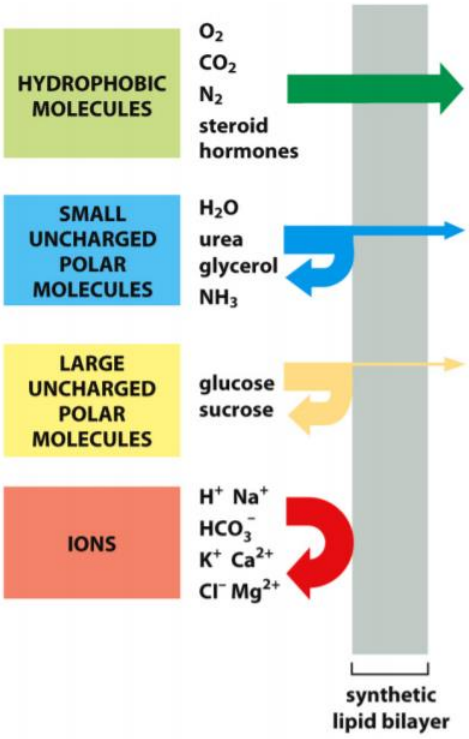
- **Most are transmembrane proteins** (crosses the entire membrane)
- Some proteins are confined to specific membrane domains in epithelial cells separated by tight junctions
    - Apical plasma membrane proteins
    - Lateral plasma membrane proteins
    - Basal plasma membrane proteins
- Some are also restricted to certain domains in non-epithelial cells
    - **Lipid rafts**
        - Cholesterol and sphingolipid rich area in outer leaflet
        - **Very rigid structures**
            - Cholesterol is stiffer than phospholipids!
    - **Caveolae**
        - Have a cave-like appearance
        - Have **small pits** of 60-80nm in diameter
        - Contain caveolin intracellular membrane proteins
        - **Important for endocytosis and signal transduction!**
- Bilayers are two-dimensional with fluid, lipids and proteins that are able to rotate and move laterally
- **Functions:**
    - Act as receptors, transporters and channels
    - For electron transport and oxidative phosphorylation
    - Controls cell-cell communication





Membrane transport:

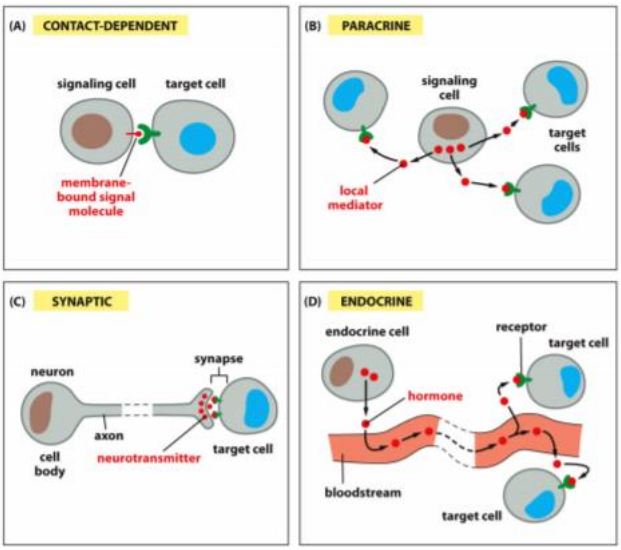
- **Transporters are asymmetrically** distributed (no pattern)
- **Small, uncharged, unionised, non-polar molecules can move directly across the lipid bilayer**
    - O_2, CO_2, steroid hormones, water, glycerol, ammonia
- Others must use transporters
    - Glucose, sucrose
    - Carriers
    - Ion channels
    - Passive transport



    - Active transport
- Large molecules must use endocytosis and exocytosis
- **Active transport** requires energy to move molecules across the membrane
    - Moves against a concentration gradient
- **Passive transport** does not require energy
    - Moves with a concentration gradient
    - Can be channel-mediated and transporter-mediated
- **Transporters**
    - Can be **active or passive transport!**
    - Bind a solute
    - Conformational shape change (reversible)
    - Expose solute to the other side of the membrane
- **Na^+/glucose co-transporter (SGLT): secondary <u>active</u> transport**
    - In **the GIT and proximal tubule**
    - Relies on the sodium gradient generated by the Na/K/ATPase active transporter!
    - **Sodium binds to the transporter allowing shape change to allow glucose to enter**
    - Both are released into intracellular environment

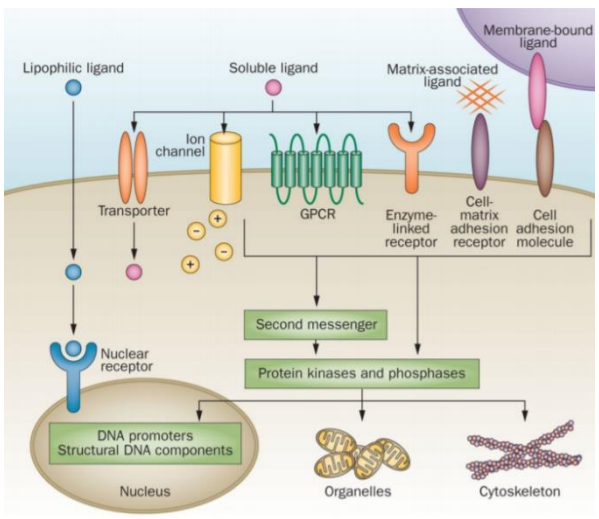
Cell communication:

- Cells monitor intracellular and extracellular environments and respond to conditions
- **Contact-dependent** uses membrane bound signal molecules interacting with another membrane bound ligand
- **Paracrine** uses local mediators
- **Synaptic** uses neurotransmitters down axons
- **Endocrine** uses hormones in the blood stream



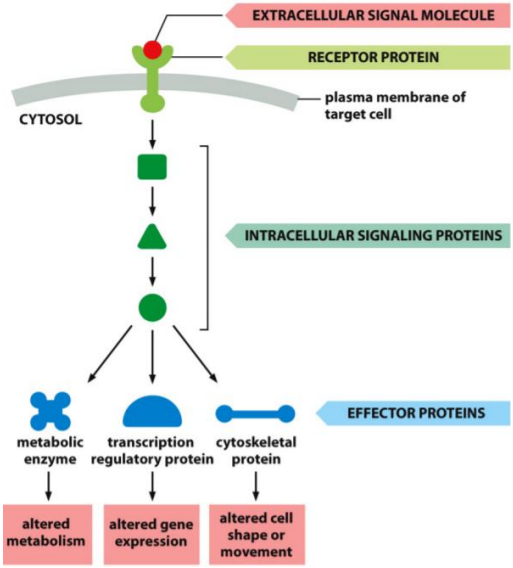
Cell receptor types (right to left)

- **Contact dependent between membrane** bound signal molecule and membrane bound ligand
- **Contact dependent** also uses membrane bound signal molecules **binding to another matrix-associated ligand**
- Enzyme linked receptor
- G-protein coupled receptors
- Ion channels
- Transporters
- Lipophilic ligands (Nuclear receptors)



Cell signalling

- Can use <u>cell surface receptors</u>
  - Usually for **large hydrophilic molecules** that cannot pass into the cell
- Can use <u>intracellular receptors</u>
  - Usually for **smaller/more lipophilic molecules**
  - Can be hydrophilic as well if they are small enough
  - Steroid hormones (oestrogen, testosterone, etc…)
- Can produce many <u>different effects</u>:
  - Acting at metabolic enzymes for **metabolism control**
  - Transcription regulatory proteins for **altered gene expression**
  - Cytoskeletal proteins for altered cell **shape and movement**
- <u>Respond to many different signals that can occur simultaneously</u>
  - Survival signals
  - Grow and divide signals
  - Differentiation signals
  - Death from signals (apoptosis) or lack of signals



Intracellular signalling

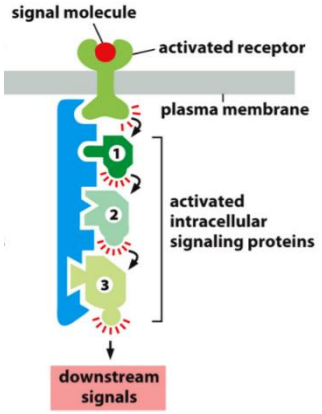
- <u>Signalling molecules can have different effects at different receptor cell types</u>
  - ACh can decrease heart rate in muscarinic heart pacemaker cells
  - ACh can increase secretion of salivary amylase at muscarinic salivary glands
  - ACh can cause muscle contraction at nicotinic skeletal muscle
- Often act **via phosphorylation**
  - Protein kinase adds a phosphate to activate the molecule
  - Protein phosphatase removes the phosphate and inactivates the cell
- Can act **via GTP binding**
  - Activated when **GDP is phosphorylated to GTP** and binds to the cell
  - GTP hydrolysis will inactivate the cell

Membrane receptors

- <u>Ligand gated ion channels (ionotropic receptors)</u>
  - Specific for certain ions due to the **selectivity filter**
  - Generally, have a narrower end on the outside of the channel to restrict movement
  - **Bind a signal molecule that activates the channel to allow ions to cross**
  - **GABA receptor = Cl^- channel**
    - Inhibits action potentials

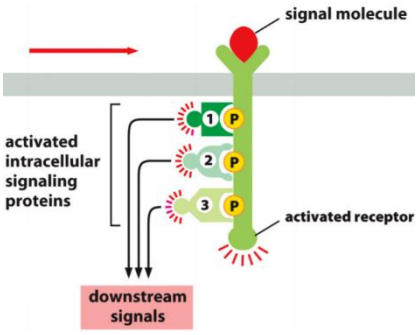
- **Nicotinic ACh receptor = cation channel**

- G protein-coupled receptors
  - **7 transmembrane** domain receptors
  - Bind to trimeric G-protein
    - α-Subunit
    - β-Subunit
    - γ-Subunit
  - GDP bound when inactive
  - GTP binds when activated to begin signal transduction
  - Muscarinic receptor is an example
- Enzyme-linked receptors
  - **Catalytic receptors**
  - Ligand binding activates the receptor
  - **Tyrosine kinase receptors (RTK) causes dimerization during activation**
    - EGFR, GFR, Toll-like receptors, **RTK, natriuretic peptide receptor**
  - NPRS example (natriuretic peptide R)
    - When activated binds to guanylyl cyclase to produce cGMP



Signalling complexes

- Scaffolding proteins
  - Hold many different proteins from a particular pathway together
  - **Rapidly speeds up the signal** since all proteins are next to each other
  - **Avoids incorrect signals from cross-overs** from occurring
  - **KSR (MAPKKK) and STE5 (Yeast) > later lecture!**
- Activated receptors
  - Recruit signalling proteins onto themselves
  - **Often occurs with enzyme-linked receptors**
  - When they become activated they can rapidly activate many different proteins that are all bound at once
  - **RTK recruits Grb2 and IRS-1! > later lecture!**



- Phosphoinositide docking sites
  - Phospholipid molecules are found in the plasma membrane
  - **Once the receptor is activated they will activate the phospholipids via phosphorylation**
  - Intracellular proteins will bind to these activated phospholipids and produce a downstream signal