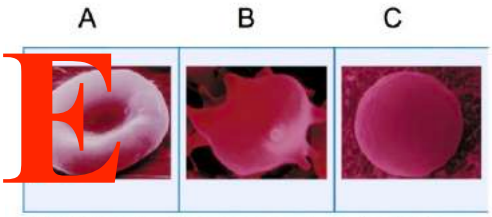
HSF2

CROSSOVER KNOWLEDGE



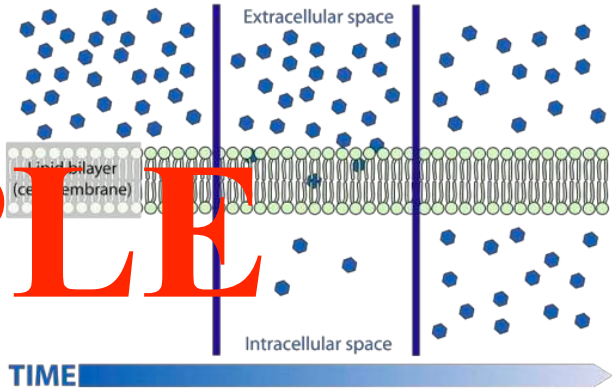
Red blood cell responses to A: isotonic, B: hypertonic and C: hypotonic solutions.

Cell Membrane

- Separates cell from environment
- Intracellular environment is different from extracellular
- Need to **control this**
- Energy needed to maintain differences
    - All cells are bathed in similar environment, control comes from moderating gateway (whatever fits inside the channel - select entities (size, charge (gatekeepers for alignment) etc.)
    - Active transport, against gradient or with gradient (cleavage of ATP used)

Permeability of Membrane

- Molecules that pass:
    - Lipid soluble
    - Uncharged
    - Small
        - Lipids, water, O_2, CO_2
- Molecules that stop:
    - Lipid insoluble
    - Charged
    - Large
        - Ions, proteins

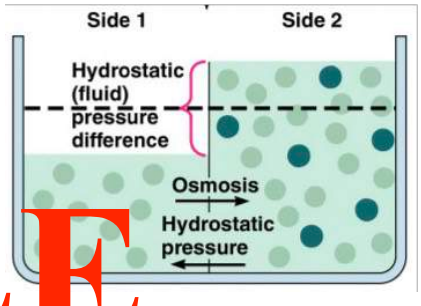


Diffusion

- Passive process
- Spontaneous
- Solutes 'flow downhill' with concentration gradient
- Net movement to eliminate concentration gradients

Osmolarity

- The total concentrations of solutes, **penetrating and non-penetrating**
    - Penetrating (pass membrane)
    - Osmolarity: count it, substance that dissociates (total) - counting particles
- Normal cell osmolarity is approximately 300 mOs



Tonicity

- Reflects cell behaviour and depends on the concentration of only the non- penetrating solutes
- Always in reference of the extracellular non-penetrating solute concentration compared to the cell's non-penetrating solutes.
- A solution can be isotonic, hypertonic or hypotonic with respect to the cell
- No units, it is a description of cell behaviour
    - RBC are poor regulators of cell volume, water has left the cell in B (inside the cell to outside, along the gradient, solute concentration is higher where the water is lower)

Lecture 36 Summary – Blood and Pressure

Terminology

- Systolic BP: **MAX pressure** exerted in arteries, blood ejected into them during systole
- Diastolic BP: **MIN pressure**, when blood drained off into remainder of vessels during diastole
- Pulse P: **ΔSBP and DBP**, measure of strength of pressure wave
- MAP: **Average pressure** responsible for **driving blood forward in tissues during CC** = DBP + 1/3 PP
  - Loss of energy due to friction, difference reduces to zero by capillaries
  - Essential for efficient function and life
  - MAP = TPR x CO = TPR x HR x SV
- CO = volume of blood pumped by one ventricle in a given time period = HR x SV
- SV = amount of blood pumped by one ventricle during a contraction, affected by **length of muscle fibre, venous return** (volume of blood at start of contraction)**, contractility of heart** (neural influences, balance b/w PNS/SNS)
  - Frank-Starling Law → increased venous return → stretch determines sarcomere length → increased force → increased SV
  - SNS → released NA → cause ↑Ca^{2+} = ↑contraction
- End-diastolic volume
  - Determined by **venous return** (skeletal muscle pump, respiratory pump, neural control (SNS tone, vasoconstriction degree)
- HR = intrinsic rate of depolarisation of autorhythmic pacemaker cells, with SA determines CO, with extrinsic NS control
  - SNS → changes ion permeability, depolarises, reaches threshold sooner, β-adrenoceptors by NA
    - **Enhance conduction of APs through AV node**
  - PNS → changes ion permeability, hyperpolarises, longer time to threshold, M_2 receptors by ACh
    - **Slows conduction of APs through AV node**

Baroreflex

In response to standing, the baroreceptors which are stretch sensitive are activated less (due to the increased blood flow to the feet, and venous return decreases) therefore firing less action potentials to brain. They are located in carotid sinus and in the aortic arch. The medulla in the brain interprets this to indicate there is too little blood flow, reacting to decrease the parasympathetic and increasing the sympathetic responses to elevate TPR and CO via increasing HR, arterial vasoconstriction and heart contractility, increasing blood pressure at heart level back to normal.

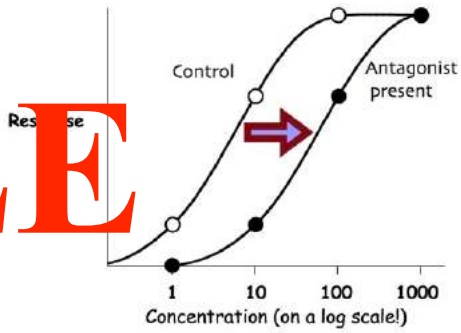
Long-term BP regulation

- Mainly through changes in CO (hormonal, renal) and TPR (hormonal, vascular structure)
- Renal function → increased ECF by reduced renal salt excretion to increase CO
- Increase TPR via thickening of arterial wall (hypertrophy), high levels of vasoconstrictive hormones

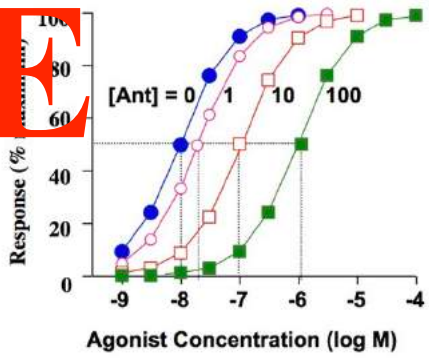
Exercise and CO

- Heart, skin, skeletal muscles and liver have increased blood flow
- Brain has constant flow
- GIT and other inactive tissues have reduced flow
- Autonomic NS has general vasoconstriction through α_1 adrenoceptor activation, selective dilatation of certain active skeletal muscles through β_2 receptors in arterial smooth muscle via local activity (metabolites such as ↑CO_2, ↓O_2, ↓pH

Competitive (surmountable) antagonism

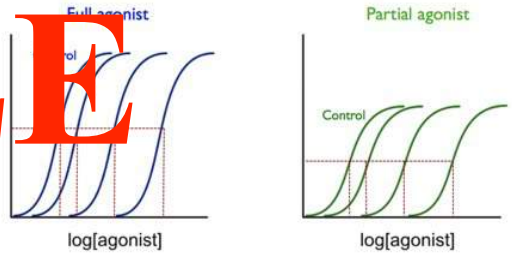


- Competitive antagonists (also known as surmountable antagonists) reversibly bind to receptors at the same binding site (active site) as the endogenous ligand / agonist, but without activating the receptor.
- Agonists and antagonists "compete" for the same binding site on the receptor. Once bound, an antagonist will block agonist binding.
- High concentrations of a competitive agonist will increase the proportion of receptors that the agonist occupies, higher concentrations of the antagonist will be required to obtain the same degree of binding site occupancy.
    - Appears to be a right-ward shift of the control curve, having the antagonist present means the agonist is less potent (require more drug to elicit the same effect)
- In functional assays using competitive antagonists a parallel rightward shifts of agonist dose–response curves with no alteration of the maximal response is observed.



- *Consequential effect of increasing antagonist concentrations*
    - Parallel, rightward shift
    - Surmountable, maximum unchanged
    - Reducing the potency, more agonist for same effect

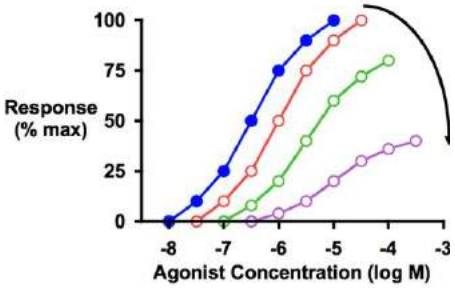
- *Consistent antagonism by competitive surmountable antagonists*
    - Same antagonist elicits similar effects to full and partial agonists acting at the same receptor
    - Relative shifts (concentration ratios) used for determining antagonist affinity and potency



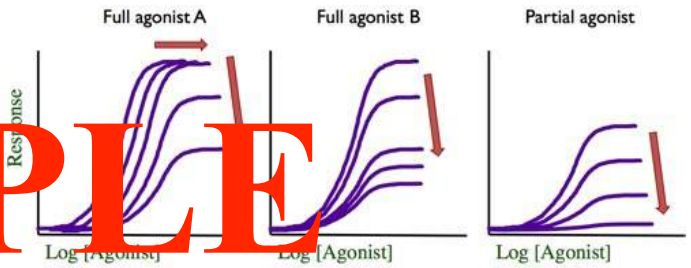
- *Antagonist affinity and potency*
    - Dissociation constant (K_D/K_B) can be derived from:
        - Direct binding assays (labelled drug required)
        - Schild plot
            - Plot of the relative shift of the agonist curve against antagonist concentration
                - Competitive antagonist occurs with a linear plot of gradient 1
            - pA_2 is the negative log of the concentration of antagonist required to cause a two-fold rightward shift of the agonist concentration-response curve
            - Indication of antagonist potency
            - pA_2 approximates pK_B (upper limit)

Non-surmountable antagonists

- Seen for competitive AND non-competitive antagonists
- Non-competitive work by changing the active site/receptor by acting on another site of the receptor or possibly another molecule
- Shape of graph changes where the **maximum depresses, rightward shift, not parallel anymore**

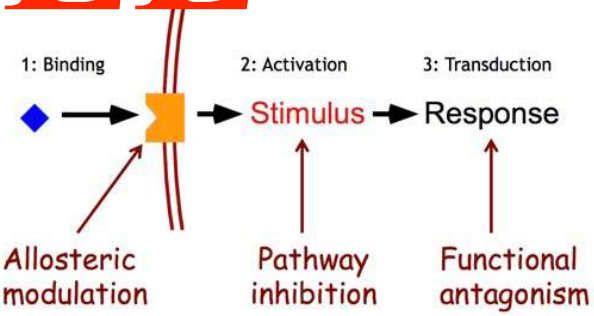


Competitive insurmountable antagonists



- Different antagonism
- Same antagonist elicits different effects on full and partial agonists acting at the same receptor
- Maximum collapses immediately if no spare receptors (i.e receptors are full, or when dealing with partial agonists)
- Process:
  - Agonist and antagonist bind to the same site
  - Pattern of antagonism is determined by
    - Association/dissociation constants
    - Relative concentrations
    - Duration of exposure
  - Binding of antagonist is slowly reversible/irreversible
    - Strong binding, very high affinity
    - Antagonist effectively decreases the number of receptors

Non-competitive antagonism



- Used to describe two distinct phenomena: one in which the antagonist binds to the active site of the receptor/inhibits part of a pathway, and one in which the antagonist binds to an allosteric site of the receptor.
- While the mechanism of antagonism is different in both of these phenomena, they are both called "non-competitive" because the end-results of each are functionally very similar. Unlike competitive antagonists, which affect the amount of agonist necessary to achieve a maximal response but do not affect the magnitude of that maximal response, non-competitive antagonists reduce the magnitude of the maximum response that can be attained by any amount of agonist.
- This property earns them the name "non-competitive" because their effects cannot be negated, no matter how much agonist is present.
- In functional assays of non-competitive antagonists, depression of the maximal response of agonist dose-response curves, and in some cases, rightward shifts, is produced.
- The rightward shift will occur as a result of a receptor reserve (also known as spare receptors, see in pharmacodynamics) and inhibition of the agonist response will only occur when this reserve is depleted

- *Type 1: Non-competitive pathway inhibition*
  - β-adrenoceptor signalling pathway can be exploited as various spots to reduce the increase in cardiac rate
  - Whether it is the enzyme targeting of adenylate cyclase, cAMP, protein kinase A, or ion channels, there are number of points that can prevent/inhibit the response