Lecture 3: How Do Drugs Act?

Drugs do not act unless bound, they have their own affinities, which allow them to bind to:

- Enzymes
- Carrier molecules
- Ion channels
- Receptors
- DNA

RECEPTORS:

- Bind to endogenous and exogenous chemicals
- Can be activated even at low concentrations
- Are on the cell surface (accessible)
- Selectivity of the target determines the specific responses observed
- They work through cell signalling molecules and altering cell function in a certain way through cascading and amplification

AGONISTS

drugs that bind and activate the receptor to illicit a response within the cell (K_A)

ANTAGONISTS

Bind, but do not activate – generally block the endogenous substance form binding (K_B)

- both types have affinity e.g. covalent, van der Waals
- the rate of the chemical reaction is proportional to the concentration of reactants

REVERSIBLE BINDING

$$[D]+[R] \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} [DR]$$

- many drugs bind reversibly and covalently
- Forward Rate: [D] x [R] x k_{+1}
- Backward Rate: [DR] x k_{-1}

*It is always assumed that the drug is presence in excess of the receptor

DISSOCIATION CONSTANT

- $k_{-1}/ k_{+1} = K_D$
- K_D = [D] 50% of the receptors are bound, ↓ K_D = ↑ affinity
- K_D is constant for a given drug-receptor combination

K_D	1 x 10^{-9}	3 x 10^{-9}	1 x 10^{-8}
$\log K_D$	-9	-8.5	-8
pK_D	9	8.5	8

CONCENTRATION CAN DETERMINE DOSE

- The concentration of a drug can determine its relative effect, the selectivity of the target determines specificity

MEMBRANE STABILISATION

- Occurs non-specifically at high concentration. This is because the receptors on the cell surface are flooded/ saturated

CONCENTRATION AND DOSE

Concentration

- Amount in a given volume
- Amount at molecular target
- Activity shown in a concentration response curve

Dose

- In-vitro: dose ≈ concentration (amount administered)
- In vivo: dose ≠ concentration

TYPES OF RESPONSE

Cellular

- Intracellular calcium
- Enzyme activity (phosphorylation, nitrosylation)
- Gene transcription

Tissue/Organ

- Contraction/ Relaxation
- Secretion

Whole Animal

- Movement/Consciousness

PLOTTING CONCENTRATION-REPSONSE DATA

- Often, radioactive compounds and fluorescent markers are used to gather data for concentration response curves
- Increasing concentrations can show increased responses
- **EC_{50}** and **pEC_{50}** are both measures of drug potency (↑pEC_{50} = ↑potency)

AFFINITY

- attraction between drug and receptor

POTENCY:

- how much of a drug is required for an effect
- Often, more potent drugs are preferred as smaller concentrations are required to illicit a response – at higher doses, there is a greater probability of unwanted responses
- Illustrated by the placement of the curve, left = more potent
- Specific and relative to each drug's own response curve

EFFECT:

- Size of the concentration response curve 'how big'

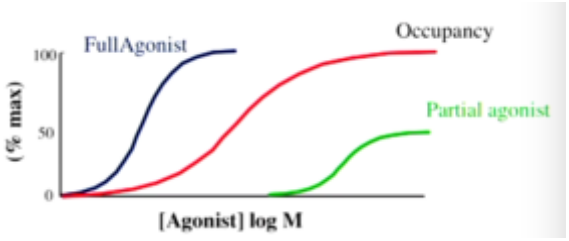
TYPES OF AGONISTS

Full Agonists

- Bind and elicit a maximal response
- Not all receptors need to be occupied for a maximum response
- Switches on effectively and efficiently
- Have a 'receptor reserve'
- Small amount can equate to a large response

Partial Agonists

- Bind and do not elicit a maximal response
- All receptors need to be occupied for a maximal response
- Maximum response is less than that of a full agonist
- Not as efficient



*both drugs may have the same affinity and occupancy curves, difference is in EFFICACY

EFFICACY:

- Binding = affinity, activation = efficacy
- Ability of a drug to activate the receptor
- Different maximal responses for drugs acting at the same receptor
- Combination of receptor number and stimulus response coupling

PHARMACOLOGICAL TARGETS FOR THERAPEUTIC DRUGS

Increasing the Action of an Endogenous Substance

- Increase synthesis
- Inhibit metabolism
- Increase release
- Inhibit reuptake / breakdown
- Give drug that mimics its action

*last two methods most common

Decreasing The Action of an endogenous substance

- Inhibit synthesis
- Inhibit release
- Increase reuptake/ breakdown
- Give drug that blocks its action