Antagonists

Learning Outcomes

- Appreciate the different binding sites of different types of antagonists (competitive, non-competitive, chemical and functional)
- Understand the difference between reversible and irreversible antagonism
- Recognise how different types of antagonists modulate agonist responses
- Understand how partial agonists can act as antagonists
- Have a well-developed understanding of drug selectivity
- Understand aspects of pharmacodynamics and adverse effects which underpin choice of drug dosage

Definition of Antagonists

A molecule that interferes with the interaction of an agonist and a receptor protein or a molecule that blocks the constitutive elevated basal response of a physiological system

Types of Antagonists

- Receptor Antagonists:
    - Competitive antagonist
        - Bind to orthosteric sites
        - Reversible or irreversible
    - Non-competitive antagonist
        - Bind to allosteric site
        - Reversible or irreversible
- Non-receptor Antagonists:
    - Chemical antagonist
    - Functional antagonist

Reversible Competitive Antagonists

- Most common type in labs and clinics due to high potency and selectivity
- Binds to the agonist binding site, termed the orthosteric site, without activating the receptor
    - Prevents agonist from binding to that site
- Does not stay bound to the receptor: dissociates and rebounds continuously.
- e.g. naloxone, an opioid receptor antagonist; treat opioid overdose
- Curve is shifted parallel to the right
    - Apparent potency of the agonist is reduced
- Can be overcome with higher agonist concentrations.

- Who 'wins' the competition for receptor binding depends on

    - concentration of agonist vs antagonist
    - receptor affinity of agonist vs antagonist

- Quantifying antagonism:
    - K_B is the equilibrium dissociation constant of competitive antagonists, a measure of affinity
    - IC_{50} is the concentration of antagonist required to reduce a response to a fixed concentration of agonist by 50%
    - NOTE:
        - IC_{50} is dependent on the concentration of agonist: more agonist requires more antagonist for the same about of inhibition.
        - Inhibition curves say nothing about the type of inhibition (i.e. competitive or non-competitive, reversible or irreversible)

Irreversible Competitive Antagonists

- Bind covalently to agonist sites or dissociated very slowly
- Affects the number of available receptors at a given time point
- At high enough concentration, irreversible competitive antagonists cannot be outcompeted = insurmountable inhibition
- Mainly used as experimental tool with few drugs used clinically
- e.g. phenoxybenzamine: covalently binds to α-adrenoceptors (non-selectively) and block the effects of catecholamines; for treatment of pheochromocytoma

- Rightward shift with increasing concentration
- Maximum reduced: insurmountable
    - May not show reduced maximum if there are spare receptors
        - May need to increase antagonist concentration to see change
- Decreased apparent potency (higher EC_{50})

Partial Agonists as Antagonists

- Can alter the response of an agonist with higher efficacy that binds to the same site
- e.g. buprenorphine: partial opioid receptor agonist; used as analgesic or to reduce opioid withdrawal symptoms
- Acts like a competitive, reversible antagonist: ↓ potency of agonist (higher EC_{50}), surmountable (=E_{max}), rightward shift with increasing concentration
- There is an initial effect of the partial agonist until the full agonist takes over after surpassing the partial agonist concentration

Non-Competitive Antagonist: Allosteric Modulation

- Binds to same receptor but has different binding site to the agonist
- Allosteric modulators influence receptor function by changing receptor conformation.

    - increasing/decreasing the affinity of agonist to orthosteric site
    - increasing/decreasing the efficacy of agonist (including skewing coupling of receptor towards different intracellular signalling pathways, termed biassed agonism)
- e.g. benzodiazepines: positive allosteric modulators of $GABA_A$ receptor (inhibitory transmitter); causes anxiolytic, sedative and anticonvulsant effects

Chemical Antagonists

- Bind directly to or destroy ligands, preventing them from binding to their targets.
- Uncommon among small molecule drugs (e.g. protamine to neutralise heparin; used for cardiac surgery), common for therapeutic antibodies (e.g. mepolizumab, anti-IL-5 antibody; anti-asthma effects)
- e.g. PROTACs (proteolysis-targeting chimeras): bifunctional small-molecules that induce ubiquitin-mediated degradation of target proteins

Functional (Physiological) Antagonists

- Oppose the biological effects of an agonist by acting at a different receptor (as an agonist)
- e.g. salbutamol: agonist at β2-adrenoceptors; causes airway smooth muscle relaxation; treat acute asthmatic attack