PCOL2605 Notes

Pharmacodynamics

Selectivity

- Drugs act selectively by binding to certain proteins only
    - Drugs are not completely selective, but can act at lower concentrations at some protein targets than others
- Limits toxic effects, and targets specific proteins that regulate a disease state
- Multi-modal drugs can simultaneously act on multiple targets
- Drug targets – Receptors, Ion channels, Carriers, Enzymes

Ion channels

- Protein gates that mediate entry/exit of ions to regulate cell membrane potential
- Voltage-gated, ligand-gated or mechano-sensitive ion channels
- Drugs – blockers or modulators (increased or decreased opening probability) of ion channels
- Local anaesthetics, e.g. lidocaine
    - Selectively inhibit pain-transmission in nerve fibres and interpretation of pain
    - Block Na^+ channels in peripheral sensory nerves to block Na^+ entry (and thus APs)
- Benzodiazepines (Diazepam) – anticonvulsant, anti-anxiety
    - GABA produced in presynaptic neuron binds to postsynaptic $GABA_A$ receptors → conformational change → increased Cl^- entry via ion channel
        - Cl^- entry into nerve cell – reduces neuronal transmission of APs
    - Diazepine – allosteric modulator (activator) of $GABA_A$ receptor channels
        - Allosteric binding of diazepine to $GABA_AR$ potentiates actions of GABA to further increase Cl^- influx into cell
        - GABA must be bound to receptor for diazepine to work

Carriers/transporters

- Drugs can block transporters to promote a beneficial therapeutic effect
- Fluoxetine (Prozac) – antidepressant
    - Selective serotonin reuptake inhibitor (SSRI)
    - Inhibits serotonin (5-HT) transporters in brain to increase [5-HT] in neuronal synapse

Enzymes

- Drugs can act as inhibitors, false substrates, or prodrugs of enzymes
- Aspirin inhibits cyclooxygenase to reduce conversion of arachidonic acid to prostaglandins
    - Reduces pain and inflammation
- Parkinson's Disease – increase dopamine to overcome loss from death of dopaminergic neurons
    - L-dopa can cross BBB unlike dopamine – bioactivated into dopamine within brain

Receptors

- Membrane or intracellular proteins that receive chemical information to regulate cell function
- Drugs – agonists or antagonists
- Cannabinoids – THC (main psychoactive constituent) is a partial agonist for CB_1 receptors in brain
    - Δ^9-THC mimics actions of anandamide (normal endogenous neurotransmitter)
    - Anandamide is released from postsynaptic receptors and act on presynaptic CB_1R
        - Inhibit Ca^{2+} channels to block *excess* release of glutamate (neurotransmitter) which can be neurotoxic – neuromodulatory/homeostatic mechanism
        - THC binds presynaptic CB_1R to mimic anandamide to offset neurotoxicity
- Rimonabant – CB_1 antagonist, blocks endogenous neurotransmission of anandamide

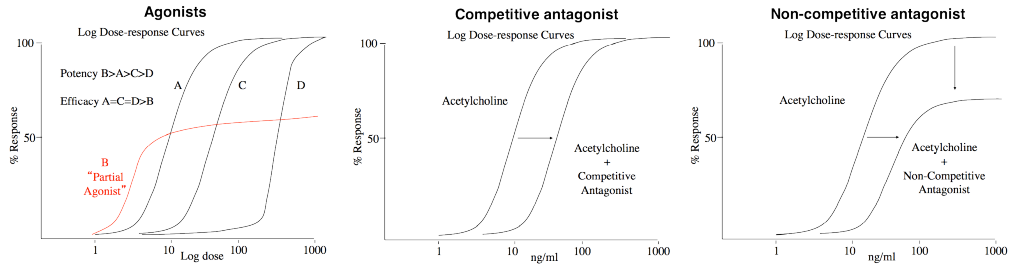
Agonists

- Direct or indirect (via transduction mechanisms, G-protein coupling) effects
- Characterised by affinity (K_D) and intrinsic activity (efficacy/ability to alter cellular function)
    - Affinity depends on association (K_1) and dissociation (K_{-1}) rate of drug-receptor complex
        - Binding forces – electrostatic, hydrogen bonding, Van der Waals, covalent
- Affinity does not equal potency, as intrinsic activity must be taken into account ($K_D \neq EC_{50}$)
    - K_D = [ligand] that gives half occupancy of receptors to form ligand-receptor complex
    - EC_{50} = effective concentration that gives half-maximal response
- Agonists can be endogenous (from body) or exogenous
    - ACh – endogenous, released from nerves, activates nicotinic and muscarinic receptors
    - Adrenaline – released from adrenal medulla, activates α/β-adrenoreceptors
- Log-scale dose-response curves – enables comparison of occupancy and potency relationships
    - Parallel curves for drugs that act similarly

Antagonists

- Antagonists – no effect/intrinsic activity, block endogenous mediators
- Atropine – selective muscarinic antagonist

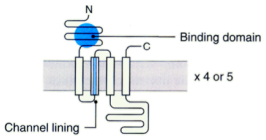
Competitive antagonist	**Non-competitive antagonist**
Parallel shift of agonist dose-response curve to the right	Non-parallel shift of agonist curve to right
	Reduces maximal effect of agonist
Can be overcome by high [agonist]	Cannot be overcome by high [agonist]



Drug-receptor interactions

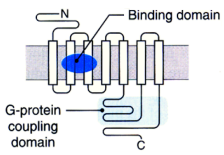
Receptors	**Location**	**Effector**	**Coupling**	**Examples**
Ligand-gated ion channels	Membrane	Channel (V_m)	Direct	nAChR, $GABA_AR$
G-protein coupled receptors	Membrane	Enzyme/channel	G-protein	mAChR, CB_1R
Kinase-linked receptors	Membrane	Enzyme	Direct/indirect	Insulin, GF
Intracellular receptors	Intracellular	Gene transcription	Via DNA	Steroid/thyroid

Ligand-gated ion channels (ionotropic)



- Contain ~20 transmembrane segments
- Surrounds a central aqueous channel through which ions selectively pass
- Mediate fast synaptic transmission (milliseconds)
- Alter electrical excitability of membranes to make APs more or less likely
- ACh must bind both binding sites to cause conformational change in nAChR, to enable Na^+ entry

G-protein coupled receptors (metabotropic)



- Contain 7 transmembrane domains, linked to a G-protein
    - Linked to either ion channel or different enzymatic pathways
- G_s – stimulatory; G_I – inhibitory
- Mediate slow synaptic/neuro-transmission (seconds)
- Agonist binds receptor → linked G-protein mobilises effector → affects ion channel or enzyme
    - E.g. Cannabinoids
        - Block Ca^{2+} entry into cell – decreased release of neurotransmitters
        - Open K^+ channels causing exiting – decreased firing/transmission of impulse