PHA3011
Principles of Drug Action

Drug Targets

Drugs

Any chemical that affects living tissues by producing a biological effect

- Endogenous or xenobiotics
- Therapeutic or drugs of abuse
- Toxic
- Natural, synesthetic or semi synthetic (begin with natural and then recreate it)

Medicine

A formulated preparation administered to produce a therapeutic effect

- Contains the active drug
- May include more than on drug
- Contains excipients, stabilisers, solvents

Ending	Class	Example/s
-olol	β-adrenoceptor blocker	propranolol; atenolol
-caine	local anaesthetic	lignocaine; bupivacaine
-dipine	Ca++ channel blocker	nifedipine
-mab	monoclonal antibodies	basilixamab; abciximab
-pril	ACE inhibitors	captopril; quinalapril
-statin	HMG-CoA reductase inhibitors	simvastatin; pravastatin
-azoles	antifungal agents	ketoconazole; miconazole

Drug Nomenclature

Individual Drug – Chemical Name
Non-proprietary – Generic Name
Proprietary – Trade/Brand Name

Drug Classification

1. Therapeutic Use – Bronchodilator, antihypertensive
2. Mode of Action – ACE inhibitor
3. Molecular Structure – Penicillins, Statins

Drug Receptor Effect

Binding of a ligand is dependent on:

- Shape
- Size

Affinity

Ability of a drug to bind to its target

Forces of Attraction

- Electrostatic (weak) – Dynamic interaction as it jumps on and off receptor
- Covalent (strong)

Affinity – Selective vs. Non-selective

- Ability to bind to many receptors but prefers one over another
- This is dependent on **dose**

Molecular Targets

- Receptors
- Ion channels
- Enzymes
- Carrier/transporters

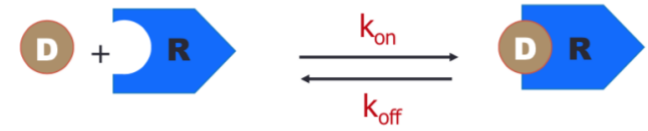
Drug Receptor Binding

For reversible binding, it follows the **Law of Mass Action**

- The concentration of drug and receptor complex is dependent on:
- Concentration of drug and receptor

Rate of Association
K(on) = [D] X [R]

Rate of Dissociation
K(off) = [DR]



At equilibrium:
K(on)[D][R] = K(off) [DR]

Drug Receptor Binding – Affinity

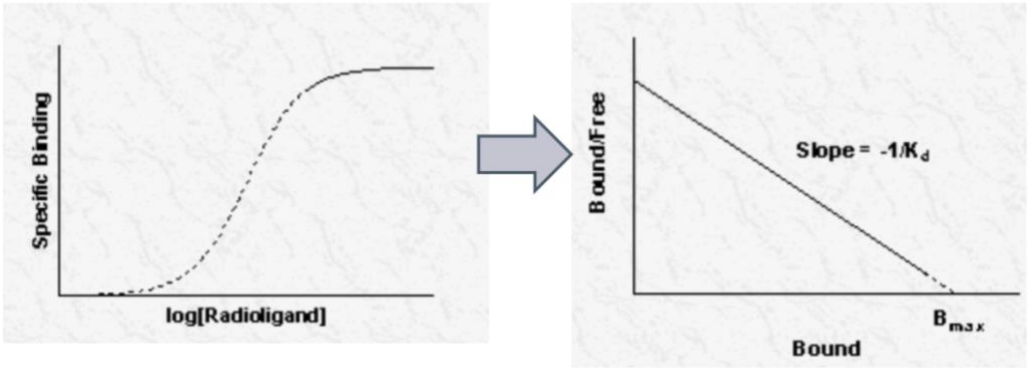
- When 50% of receptors bound
- [R] = [DR] = [D] = Kd
- Kd = Equilibrium dissociation constant

$$\frac{[D]*[R]}{[DR]} = \frac{k_{off}}{k_{on}} = K_d$$ = equilibrium dissociation constant *(units of concentration)*

Small Kd = Less concentration needed = Greater Affinity
Large Kd= More concentration needed for same response = Less Affinity

Saturation Binding Experiments

- Radiolabelled 'test' ligand is added
- Measure specific binding with increased tagged ligand
- Determine receptor density (Bmax) and Affinity (Kd)

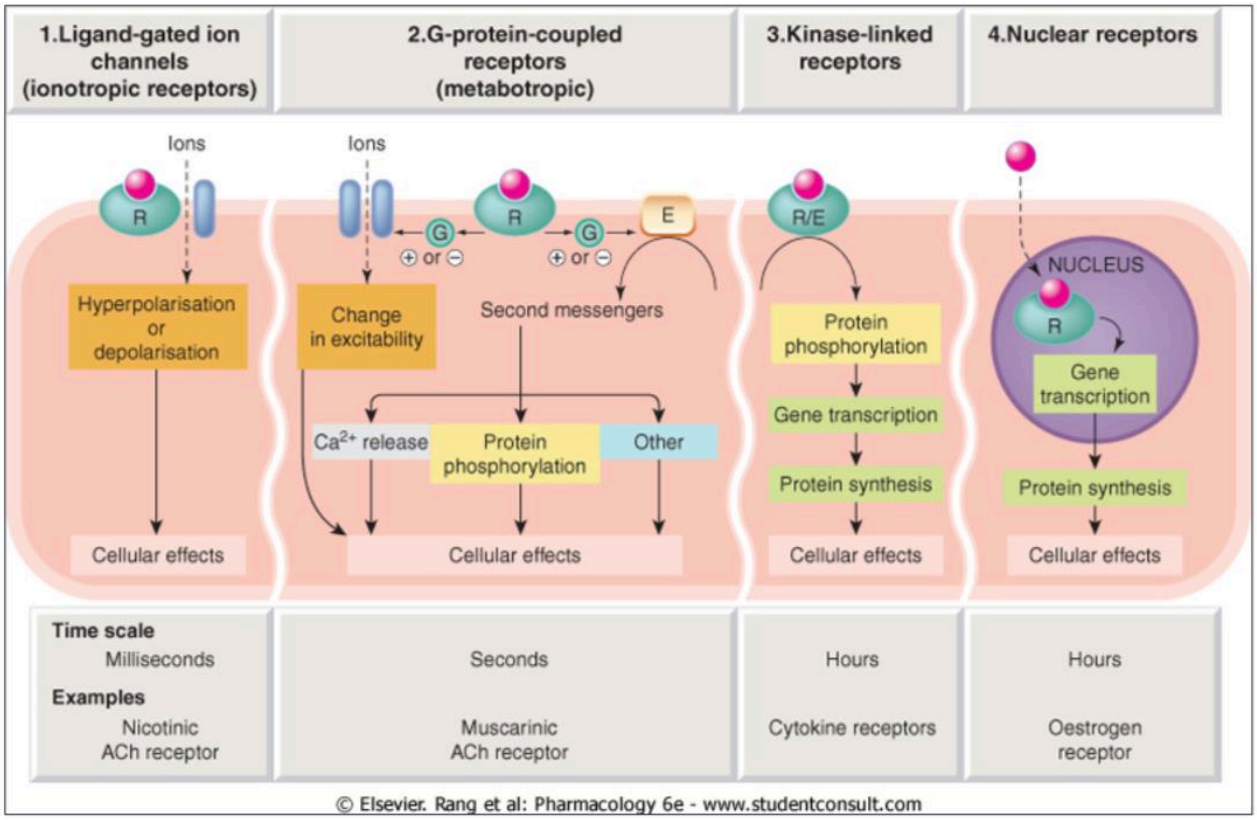


Competition Binding Experiments

- Receptor preparation for when we don't want to tag our ligand as it may effect response, rather labelling the antagonist to measure IC50
- Single labelled known antagonist
- Unlabelled test ligand
- Measures inhibition of binding [labelled ligand] by the [unlabelled ligand]
- Smaller IC50 = Greater Affinity as less drug is needed to bind and cause response

Steps for a Drug

Binding → Activation → Transduction



Agonism

Efficacy = Ability to cause activation E=1

- Full agonists have an efficacy of E=1
- Antagonists have no efficacy E=0 but have affinity, as they oppose the actions of endogenous/exogenous agonists

agonist $D + R \rightleftarrows DR \rightleftarrows R^*$

receptor antagonist $D + R \rightleftarrows DR \not\rightleftarrows R^*$

Increase Dose = Increase Response

Clinical Efficacy

- The efficacy to produce therapeutic outcomes

Law of Mass Action

- Amount of DR complex depends on [D] and [R}
- Magnitude of response is dependent on the number of DR complexes
- Threshold on a concentration response curve, is the first point of change

Potency

Is a measure of how much drug is needed to cause an affect.

- Lower concentration with the same or greater response = Increased potency
- Measured using EC50 or pEC50 = this is a negative log
- Therefore, larger pEC50's will mean a lower concentration and therefore, greater potency

Current Occupational Theory Model

Determined by

1. **Number of receptors and how well the receptors cause a response**
2. **The intrinsic efficacy of the drug**

Partial Agonist – Have affinity, but lower efficacy as a it requires a greater number of receptors to occupy to produce the same or lower maximum response

Full Agonist – Can produce a maximal response whilst occupying fewer than 100% of receptors

Drug	Mechanism
Glutamate and GABA	Type I Simple amino acids - Fast
N.A/5-HT/Adr	Type II Catecholamines - slower
Oxyocin	Type III Neuropeptides - Slowesr
Noradrenaline	Selective for Alpha 1
Adrenaline	Selective for Beta 2 and alpha 1 at higher doses
Isopreanline	Selective Beta 2 receptor
Phenylephrine	Alpha 1 Selective agaonist
Methoxamine	
Prazosin	Alpha 1 Antagonist
Clonidine	Alpha 2 agonist
Yohimbine	Alpha 2 antagonist
Dobutamine	Beta 1 agonist
Atenolol/Metoprolol	Beta 2 antagonist
Salbutamol	Beta 2 agonist
Phentolamine	Non-selective alpha antagonist
Propranolol	Non selective beta antagonist
Acetylcholine	Muscarinic agonists
Methocholine	Susceptible, slightly and neglible to ChE
Carbechol	
Pilocarpine	Muscarinic agonists
	Neglible and not able to activate Nicotinic receptors
Atropine	Non-selective muscarinic antagonist
Pirenzepine	M1 Antagonist
Methoctramine	M2 Antagonist
Darifenacin	M3 Antagonist
Hyoscine	Muscarinic Antagonist
Suxamethonium	Nicotinic muscle agonist
	Limited degradation by cholinesterase - only in plasma
	Persistant depolarisation of motor end plate
	Therefore, new AP cannot be generare and no contraction
Tubocurarine	Nicotinic muscle antagonist
	Non-derpolarising neuromuscular blocker
	Causes histamine to be released and blocks ganglia
Edrophoinum	Only Binds at anionic site - Fast reversible - Diagnose
Neostigmine	Bonds at both - Slow irreversible
Physostigmine	Treats M.G
Sarin	Binds irreversibly to enzyme
Ecothiophate	Very lipophillic
Pralidoxime	Antidote that removes phosphate from serine O-H group
	Must be given early as enzyme undergoes chemical change
Asprin	Irreversibly COX inhibitor
Misprostil	Prophylaxis for peptic ulcers with NSAID use

Drug	Mechanism
Rofecoxib	COX 2 selective
	Inhibits PGE2 and PGI2 for inflamattion and fever/pain
	Treats R.A, and decreases stomach ulcers and bleeding
Montelukast	Leukotriene Antagonist
Mepyramine	
Diphenahydramine	H1 Antagonist - Gq - Anti-emetic
Cimetidine	H2 antagonist to decrease gastric secretion - Gs
Thiperamide	H3 antagonist - Gi/Go
Loratidine	H1 antagonist that has poor access to BBB
Ondanestron	5-HT3 antagonists in PNS and CTZ
Pizotifen	5-HT2 antagonsit to prevent a migraine
Suamtriptan	5-HT 1B/1D agonist that constrict cerebral blood vessels
	Can cause vasoconstriction in coronary (5-HT1B)
Ang III and Compound 21	Vasodilation anti-inflammatory and anti-fibrotic
Saralasin	Antagonist for AT2 receptors
Captopril	S-H binds to Zn to inavctive ACE - Orally active
Enalopril	Pro drug, converted to enalaprilat in the liver
	Decrease Ang II and Aldosterone
	Increases BK - Cough, Hypotension, hyperkalaemia
Losartan	Non-peptide antagonist for AT1 receptors
	Inhbit RAS but increase Ang II
	No change to BK - same s.e. as ACE inhibitors
Spironolactone	Aldosterone anatgonist
	Inhibits cardiac fibrosis and weak duiretic
	Hyperkalaemia
Lidocaine	Local anasthetics reversibly block Na channels
	Plugs Na channel pore and prevents pain
	Affinity for for open/inactivated, but can block resting
	Used for ventricular arrhythmias and dentistry
Tetrodoxin	Blocks sodium channels in all states
Nifedipine	Vascular selective - Hypertension
Diltiazem	Cardio and vascular selective - Angina
Verapamil	Cardioselective calcium blocker - Arrhythmias
Minoxidil	Opens K-ATP channels to lead to closure of VOCC by hyperpolarising the cell membrane - resistance BP
Glibenclamide	Closure of K-ATP channels in pancreatic beta cells causes depolarisation, calcium entry leads to insulin release
Tetraethylammonium	Blocks VOKC to open calcium entry
Apamin	Blocks K-ATP pump to keep calcium in the cell