How do drugs work? Mechanism of Drug Action and Drug Targets

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MEDICAL AND HEALTH SCIENCES

Learning Objectives

By the end of these lectures you should be able to:

1. Describe the potential drug targets within a human body
2. Describe the role of receptors, enzymes, ion channels and transporters in drug action
3. Understand how drugs bind to receptors, and define the principles of affinity, efficacy and potency
4. Understand the concentration/dose-response curve and what information can be gained from it

Learning Objectives

By the end of these lectures you should be able to:

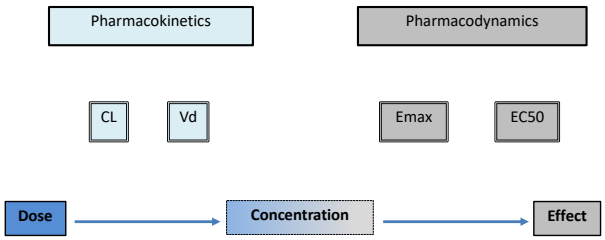
5. Differentiate between inverse agonism, agonism and antagonism
6. Differentiate between different types of antagonism and understand their impact on the concentration/dose-response curve
7. Define the term selectivity and explain its relevance to drug therapy
8. Describe receptor plasticity and explain its clinical relevance

"Drug" vs "Medicine"

- A drug is a chemical/substance that is usually used to treat a disease/condition
- When administered appropriately cause a range of physiological and biochemical/molecular changes in a complex biological system that relate to its composition, structure and target
- A medicine is used to treat a disease/condition

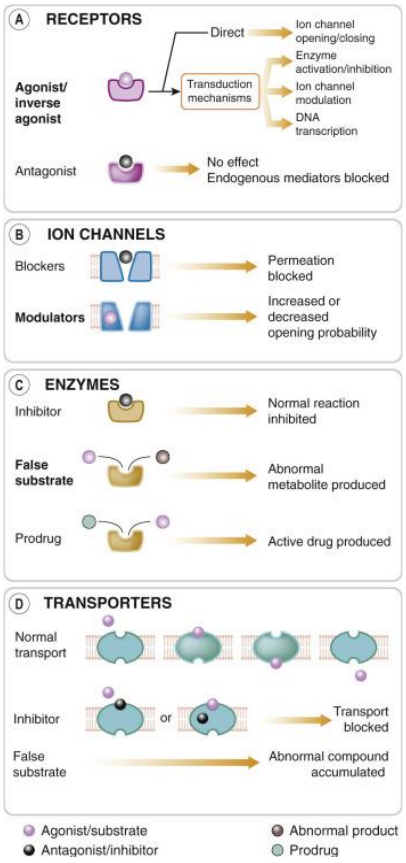
Just to clarify some terminology before progressing into the module. These definitions will not be assessed but are important when discussing pharmacology.

Dose to Effect



Mechanism of Drug Action

- Most drugs produce their effects by **binding** to protein molecules. Drug binding often leads to a conformational change in the protein. Four primary drug targets are:
  - Ion channels
  - Enzymes
  - Carrier molecules
  - Receptors
- Important exceptions are cytokines (ligand targeted by mAbs) and DNA (antitumour and antimicrobials)



Types of target for drug action.
How drugs act : molecular aspects
Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS,
Rang & Dale's Pharmacology, 3, 22-49

These targets were all covered in Biosci 107. We will focus on specific aspects relevant to pharmacology, but for more detail (broader) refer back to those course notes.

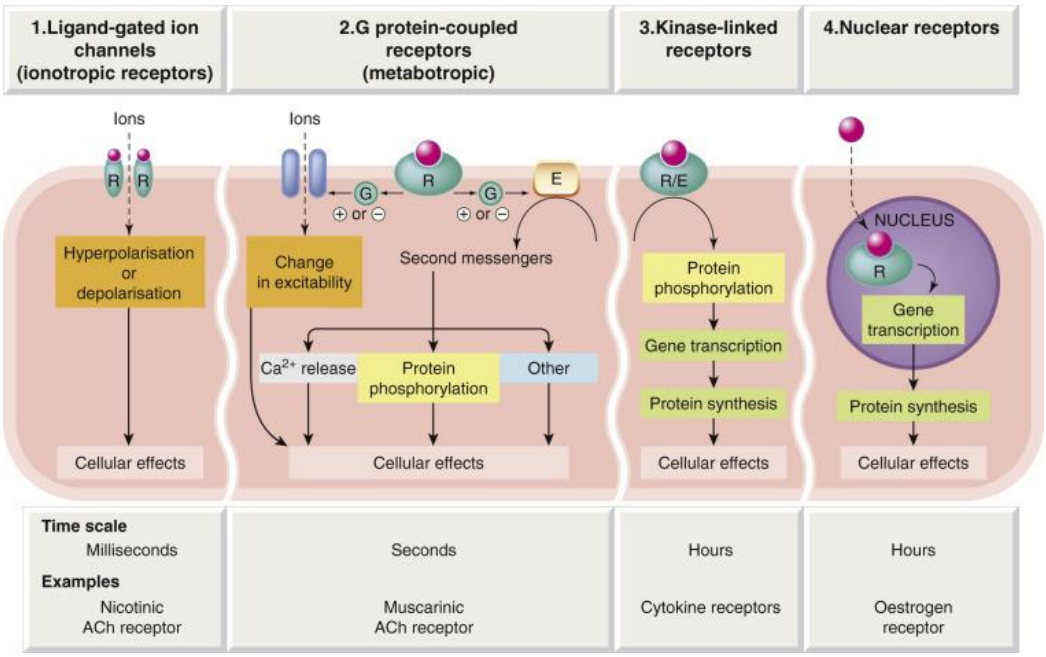
Receptors

- Proteins which specifically recognise a particular neurotransmitter/hormone and upon binding undergo a conformation change leading to activation/inhibition of cell signalling.
- Four main families of receptor:
  - Ligand Gated Ion Channels (Ionotropic receptors)
  - G-protein coupled receptors
  - Tyrosine kinase/cytokine receptors
  - Nuclear/Steroid Hormone Receptors

Receptor Terminology

- Affinity: attraction of a ligand (drug) for a receptor
- Efficacy (intrinsic activity):
  - Maximum effect = 1
  - No effect = 0
- Agonists have affinity and efficacy (mimics)
- Antagonists have affinity but no efficacy (prevents)

Signalling Pathways



Types of receptor–effector linkage. How drugs act : molecular aspects. Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 3, 22-49. Accessed via Clinical Key. Copyright © 2016

Families Of Receptors

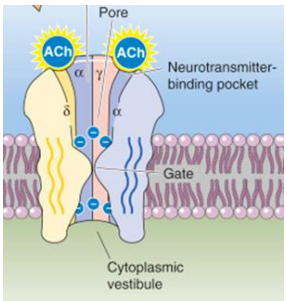
- Ligand Gated Ion Channels (Ionotropic receptors)
- G-protein coupled receptors
- Tyrosine kinase/cytokine receptors
- Nuclear/Steroid Hormone Receptors

Again, these are covered in Biosci 107, Lecture 9 – How Cells Communicate.

Ligand Gated Ion Channels

- Mediate fast signal transmission at synapses (action occurs in a fraction of a millisecond)
- All are multi-subunit complexes
- All have three important properties:
  - They are activated in response to specific ligands
  - They conduct ions through the otherwise impermeable cell membrane
  - They select among different ions

The Receptor Pore



Synaptic Transmission and the Neuromuscular Junction
Moczydlowski, Edward G., Medical Physiology, Chapter 8, 204-227.e2
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•The five TM2 helices are sharply kinked inwards halfway through the membrane forming a constriction.
•The TM2 helices are believed to snap to attention when Ach binds, opening the channel

Ionotropic Receptors As Drug Targets

- **$GABA_A$** – benzodiazepines and barbiturates (sedation and anxiolytic effects), flumazenil.

- **Glutamate** – ketamine (anaesthetic). Major target for neuroprotection and anti-convulsants, but to date all compounds have shown major adverse effects (predominantly hallucinations)

Fig. 45.3 Model of benzodiazepine/$GABA_A$-receptor interaction. Anxiolytic and hypnotic drugs
Ritter, James M., DPhil FRCP HonFBPhS FMedSci, Rang & Dale's Pharmacology, 45, 569-579

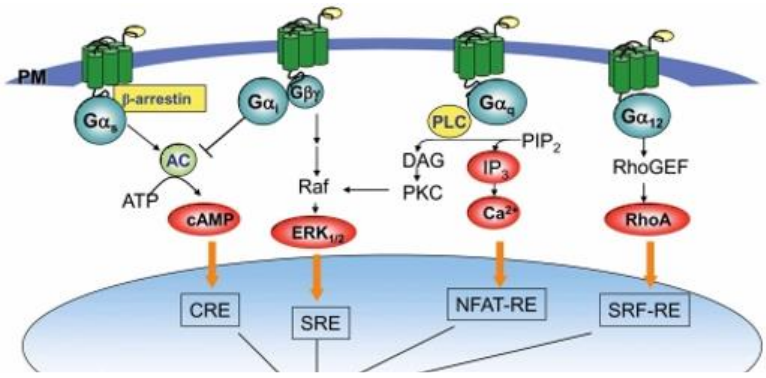
Break

- Where in the body are the ionotropic receptors we've covered?
- Why are they important in these areas?

Families Of Receptors

- Ligand Gated Ion Channels (Ionotropic receptors)
- G-protein coupled receptors
- Tyrosine kinase/cytokine receptors
- Nuclear/Steroid Hormone Receptors

Key GPCR Signalling Pathways



Cheng, Zhijie & Garvin, Denise & Paguio, Aileen & Stecha, Pete & Wood, Keith & Fan, Frank. (2010). Luciferase Reporter Assay System for Deciphering GPCR Pathways. Current chemical genomics. 4. 84-91. 10.2174/1875397301004010084.

Potential therapeutic uses of mAChR subtype-selective compounds*
From: :
***Nature Reviews Drug Discovery* 6, 721-733 (2007)**
doi:10.1038/nrd2379

Clinical condition	Drug	References‡
Alzheimer's disease Cognitive impairment	M_1, M_5 or mixed M_1/M_5 agonist; M_2 antagonist§	51,52,54–56, 58,69
Sjögren's syndrome	M_1, M_3 or mixed M_1/M_3 agonist	15,25,114
Schizophrenia	M_1, M_4 or mixed M_1/M_4 agonist	18,74,75
Parkinson's disease	M_1, M_4 or mixed M_1/M_4 antagonist	14,18,22,72
Type 2 diabetes	M_3 agonist (peripherally acting)	29
Obesity	M_3 antagonist (centrally acting)	16,129
Peptic ulcer disease‖	M_3 or mixed M_3/M_5 antagonist	116,117
OAB, COPD	M_3 antagonist	27,94,95,101
Irritable bowel syndrome Gastrointestinal spasms	M_3 or mixed M_2/M_3 antagonist	15,28,105–110
Antinociception	M_4 agonist	26
Wound healing	M_4 agonist, M_3 antagonist	121
Cerebrovascular insufficiency	M_5 agonist	19,69
Drug addiction and withdrawal	M_5 antagonist	83–85

*The proposed therapeutic uses of the indicated agents are based on gene targeting and/or pharmacological data (see text for details). ‡Note that only studies dealing with muscarinic acetylcholine receptor (*mAChR*) mutant mice have been included in this table. §Although several pharmacological studies suggest that M_2 receptor-preferring antagonists can enhance cognition in experimental animals[67,68], studies with *M2R*$^{-/-}$ mice have shown that the complete lack of M_2 receptors is associated with cognitive deficits (see text for details)[59]. ‖Note that pirenzepine and telenzepine, two M_1 receptor-preferring antagonists, are used for the treatment of peptic ulcer disease in Europe, Japan and Canada. COPD, chronic obstructive pulmonary disease; OAB, overactive bladder.

Drugs acting through GPCRs

DO NOT NEED TO LEARN THESE DRUGS*

- β-adrenoceptor – propranolol, isoprenaline
- Adenosine receptors – caffeine, theophylline
- Dopamine receptors – L-dopa, haloperidol, clozapine
- Opioid receptors – morphine, codeine
- Serotonin receptors – buspirone, clozapine, ondansetron
- Muscarinic receptors – atropine
- Cannabinoid receptors – cannabis, Sativex

** - unless they appear elsewhere in the course*

Families Of Receptors

- Ligand Gated Ion Channels (Ionotropic receptors)
- G-protein coupled receptors
- Tyrosine kinase/cytokine receptors
- Nuclear/Steroid Hormone Receptors

Tyrosine Kinase Receptors

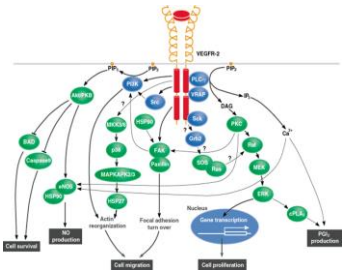
- Receptor functions as an enzyme that transfers phosphate groups from ATP to tyrosine residues on intracellular target proteins.
- Tyrosine kinase receptors mediate the actions of growth factors, cytokines and certain hormones (eg insulin).

Vascular Endothelial Growth Factor Receptors

- Essential for angiogenesis during development, pregnancy, wound healing
- Also in pathophysiological conditions eg cancer, rheumatoid arthritis, cardiovascular disease.
- Multiple receptors/multiple ligands, we will look briefly at VEGFR2

VEGFR2

- Ligand stimulated receptor dimerization and autophosphorylation, triggers pathway
- Activation serves to promote endothelial health



Matsumoto T and Claesson-Welsh L. *Science's STKE* 11 Dec 2001: Vol. 2001, Issue 112, pp. re21. DOI: 10.1126/stke.2001.112.re2

Protein Kinase Inhibitors

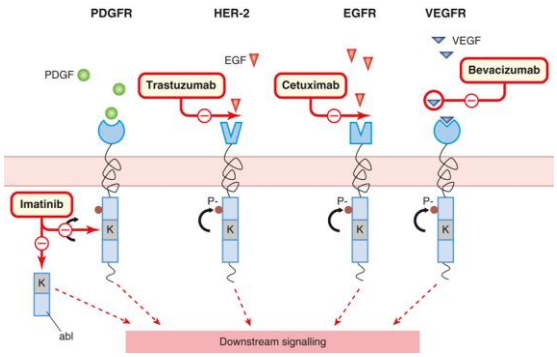
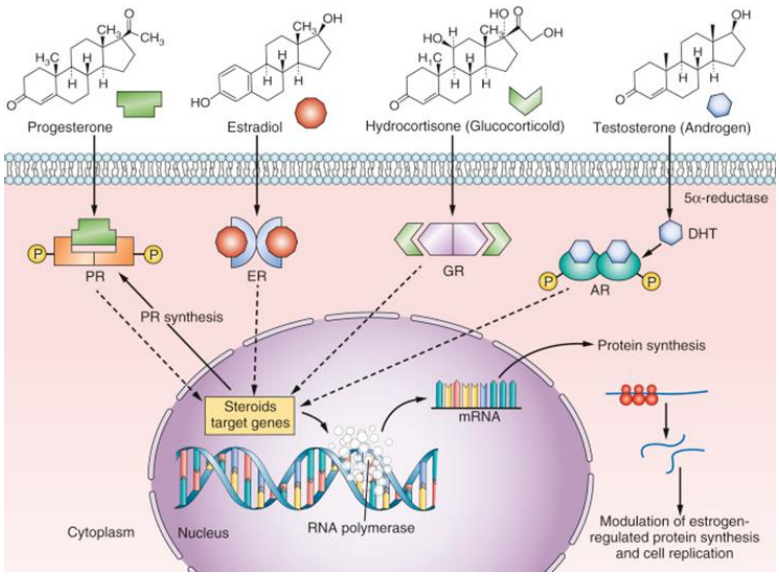


Fig 57.8. Ritter, James M., DPhil FRCP HonFBPhS FMedSci, Rang & Dale's Pharmacology, 57, 716-732

Families Of Receptors

1. Ligand Gated Ion Channels (Ionotropic receptors)
2. G-protein coupled receptors
3. Tyrosine kinase/cytokine receptors
4. Nuclear/Steroid Hormone Receptors

Nuclear Receptors



Steroid Receptors in Breast Cancer
Abderrahman, Balkees, The Breast: Comprehensive Management of Benign and Malignant Diseases, 21, 272-281.e2. Accessed via ClinicalKey 23.05.19

Estradiol = ethinylestradiol (contraception)

Activity

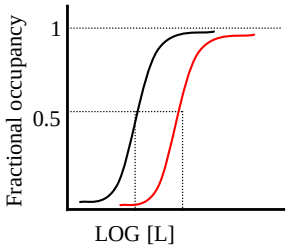
- Describe the four types of receptor within a human body
- How does their signal transduction pathway relate to their role(s) and time for action?

How do drugs bind to receptors?

- Van der Waals forces – weak forces
- Hydrogen binding – stronger
- Ionic interactions – between atoms with opposite charges, stronger than hydrogen, weaker than covalent
- Covalent binding – essentially irreversible

Affinity

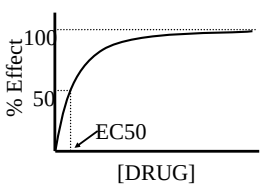
- The higher the *affinity* of the drug for the receptor, the lower the concentration at which it produces a given level of receptor occupancy.

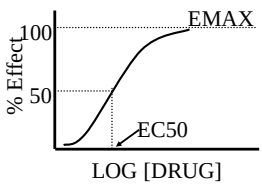


Which drug has higher affinity?

Biological Response

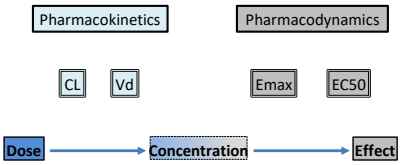
- Biological response, eg a rise in blood pressure, contraction of a strip of smooth muscle in an organ bath, or the activation of an enzyme can be measured and plotted as a concentration response curve.
- In any system the response to a drug can be classified by its EC50 and Emax

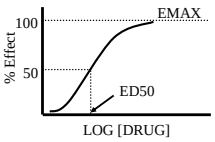




Dose vs Concentration

- Dose is the actual amount of medicine administered, concentration is what that dose produces in the body

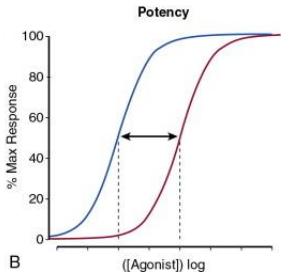


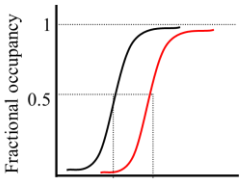


Potency

- EC_{50} is used to measure the potency of an agonist.
- EC_{50} is the effective concentration of an agonist that produces 50% of the maximal response
- The *more* potent the agonist, the *lower* the EC50.
- Antagonist potencies are more complicated to determine, but a similar principle holds.

Dose Response Curve Potency





Adapted from Vascular Pharmacology
Harrison, David G., Vascular Medicine: A Companion to Braunwald's Heart Disease, Chapter 6, 75-93

Affinity vs Biological Response

- Concentration - response curves are not a good measure of affinity because the relationship between receptor occupancy and response is not strictly proportional :
  - considerable amplification may exist - it may only take a low level of receptor occupancy to cause a maximal response in some tissues.
  - Many factors downstream from the receptor binding may interact to produce the final response.

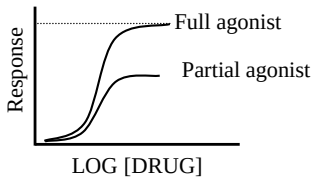
Eg Adrenaline increases cardiac output and constricts some blood vessels while dilating others, and the change in arterial pressure itself evokes a reflex response which modifies the primary response of the drug

Efficacy

- The ability of a drug to bind to a receptor and cause a change in the receptor's action is termed "efficacy" and measured by Emax
  - A drug with positive efficacy will activate a receptor to promote cellular response - ***AGONISTS***
  - A drug with negative efficacy will bind to receptors to decrease basal receptor activity - ***INVERSE AGONIST***
  - A drug with no efficacy will bind to the receptors but have no effect on activity –***ANTAGONIST*** ***(what would the effect of this be?)***

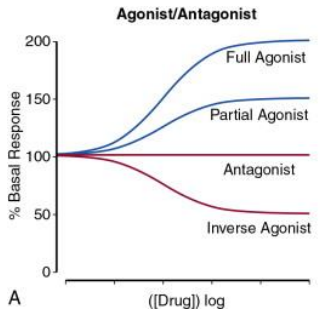
Agonism

- Drugs the elicit the maximum tissue response are *full agonists,* drugs that produce less than the maximum response are *partial agonists.*



- *Partial agonists* can not produce maximal response even at 100% receptor occupancy.

Types of Agonist: Full, Partial & Inverse



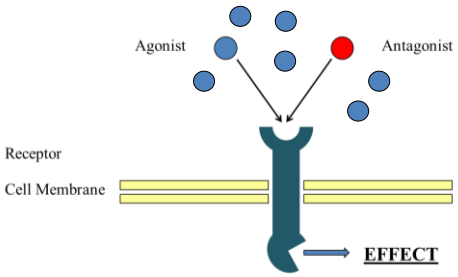
Adapted from Vascular Pharmacology
Harrison, David G., Vascular Medicine: A Companion to Braunwald's Heart Disease, Chapter 6, 75-93

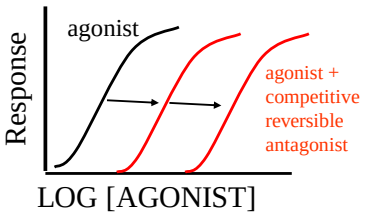
Antagonists

- A compound that binds to but does not activate (or inactivate) the receptor.
- Antagonists have affinity but NO efficacy.
- Defined by how they bind to the receptor…

Competitive Antagonism (Reversible)

- Bind to the receptor in a reversible manner to compete directly with agonist binding.
  - What effect will this have on an agonist response curve?



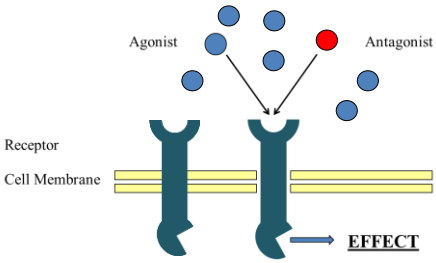


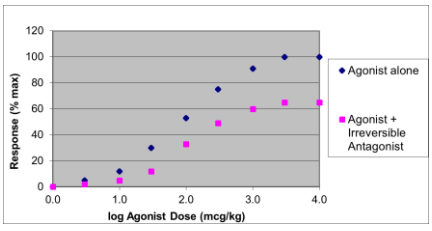
e.g. Metoprolol, naloxone, losartan

Competitive Antagonism (Irreversible)

Drug covalently binds to the receptor. Not reversible

Reduces the number of receptors available to the agonist.





Good example is clopidogrel. It's an antiplatelet that is an irreversible antagonist at P2Y12 receptors (a few in this class are irreversible).