How do drugs work? Mechanism of Drug Action and Drug Targets 2

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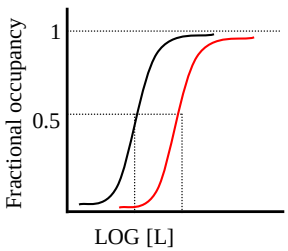
How do drugs bind to receptors?

- 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

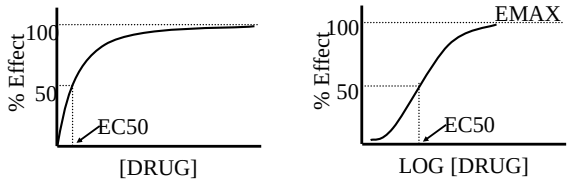
- The higher the *affinity* of the drug for the receptor, the lower the concentration at which it produces a given level of receptor occupancy.



Which drug has higher affinity?

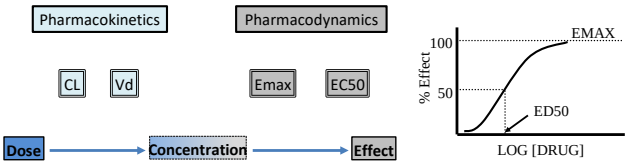
Biological Response

- 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

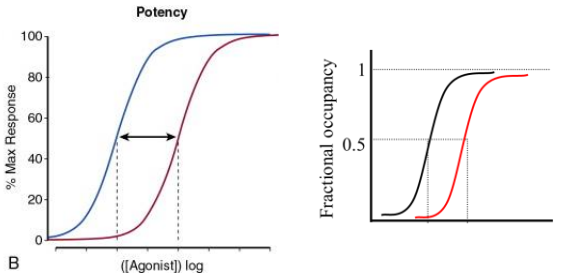
- Dose is the actual amount of medicine administered, concentration is what that dose produces in the body



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

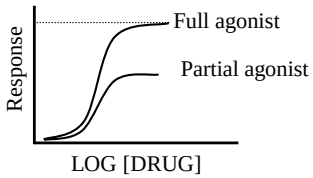
- Concentration - response curves are not a good measure of affinity because the relationship between receptor occupancy and response is not strictly proportional :
  - considerable amplification may exist - it may only take a low level of receptor occupancy to cause a maximal response in some tissues.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

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?)***

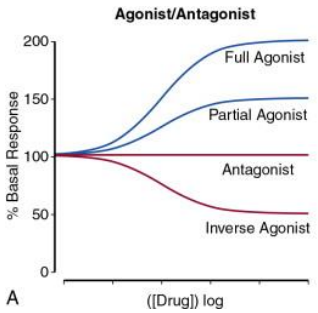
Agonism

- 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



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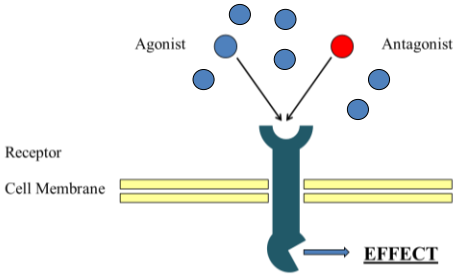
Harrison, David G., Vascular Medicine: A Companion to Braunwald's Heart Disease, Chapter 6, 75-93

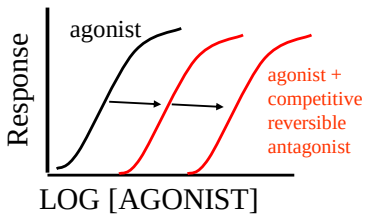
Antagonists

- 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?



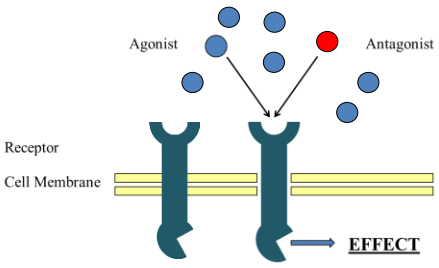


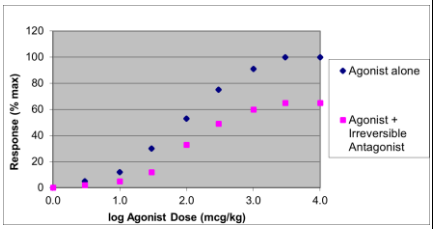
e.g. Metoprolol, naloxone, losartan

Competitive Antagonism
(Irreversible)

Drug covalently binds to the receptor. Not reversible

Reduces the number of receptors available to the agonist.



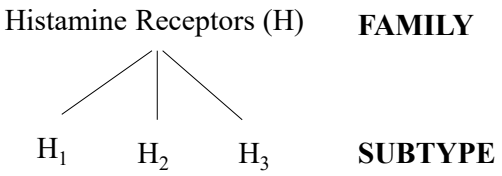


Good example is clopidogrel. It's an antiplatelet that is an irreversible antagonist at P2Y12 receptors (a few in this class are irreversible).

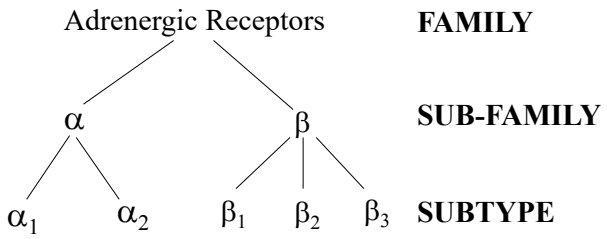
Break

- Construct your own summary table for the types of antagonism
  - What are their key properties?
  - How are they similar?
  - How are they different?
- Which type of antagonist is least likely to be commonly used? Why?
- Which type of antagonist is likely to be the most commonly used? Why?

Receptor Terminology



Receptor Terminology



Biosci 107 Lecture 6 – Autocrine and Endocrine 2 has significant description of what happens during SNS activation, but no specifics about receptors.

Selectivity for Subtypes

- Preferential binding to a certain subtype leads to a greater effect at that subtype than others
  e.g. salbutamol at β_2 (lungs) rather than β_1 (heart)
- Lack of selectivity can lead to unwanted drug effects
  e.g. fenoterol
- Selectivity for H1 receptors is how current antihistamines work
  e.g. fexofenadine

Antipsychotic Medications

- Typical vs atypical antipsychotics
- Typical
  - Dopamine antagonists
  - e.g. haloperidol
- Atypical
  - Dopamine and 5HT antagonists
  - e.g. quetiapine

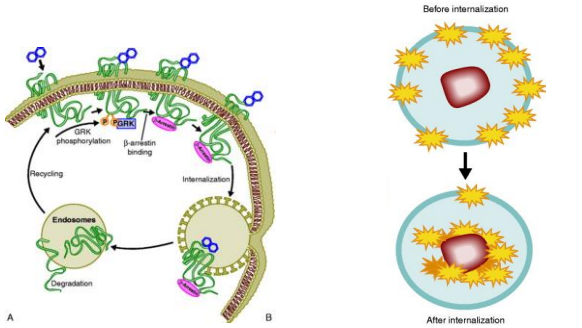
Receptor Plasticity

- Receptor states and populations do not remain constant over time
- This plasticity is largely responsible for the changes that occur in effectiveness of chronic drug (or endogenous compound) over time
  e.g. tolerance, insulin resistance

Regulation of Receptors (Receptor Plasticity)

- Changes in receptor state
  - Desensitisation / Exhaustion of mediators
- Changes in receptor populations
  - Up regulation
  - Downregulation

Desensitisation & Internalisation

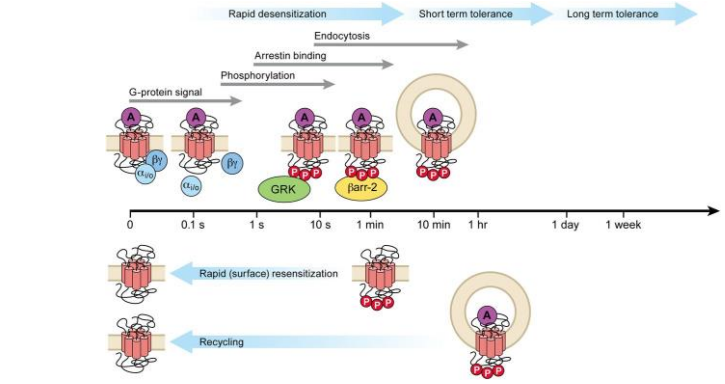


(Adapted from A Pharmacology Primer (4th ed). T Kenakin. Elsevier. 2015 (Fig 5.7)
https://www-sciencedirect-com.ezproxy.auckland.ac.nz/science/book/9780124076631

Receptor Population Changes

- Chronic <u>agonist</u> administration can lead to <u>DOWN REGULATION</u>
  - Eg chronic salbutamol can cause internalisation of receptors → less receptors available for stimulation → decreased bronchodilation
- Chronic <u>antagonist</u> administration can lead to <u>UP REGULATION</u>
  - Eg chronic propranolol can increase synthesis of β_1 receptors in the heart → less antagonism → decreased drug effect (increased HR & BP)

Desensitisation & Tolerance



Clinical Significance

- Tolerance:
  - Eg morphine, salbutamol
- Adverse Effects:
  - Eg typical antipsychotics are predominantly D_2 antagonists
- Therapeutic Effects
  - Tricyclic antidepressants

Non-Receptor Protein Targets

- Not all drugs act directly at receptors
- Some drugs act at non-receptor protein targets:
  - Enzymes (COX inhibitors)
  - Carrier proteins (TCAs & SSRIs)
  - Ion channels (local anaesthetics)
- Some drugs act at non-protein targets
  - Soluble ligands e.g. inflammatory mediators
  - DNA

Enzymes As Drug Targets

- Cyclooxygenase and NSAIDs (e.g. ibuprofen) – used to treat pain and inflammation
- HMG CoA Reductase and Statins (e.g. simvastatin) – used for lowering cholesterol

Effects of Prostanoids

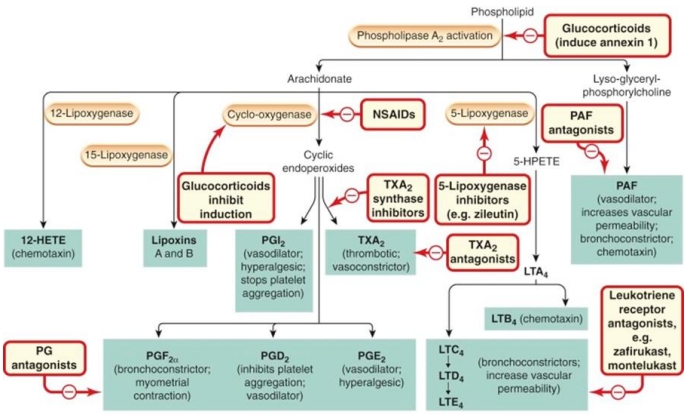


Figure 17.1 - Local hormones 1 : histamine and the biologically active lipids
Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 17, 212-221
Accessed via Clinical Key. Copyright © 2016 © 2016, Elsevier Ltd

Effects of Cyclooxygenase Inhibition

- NSAID inhibition of both COX 1 and COX 2 leads to:
  - ↓ inflammation
  - ↓ pain
  - ↓ fever
  - But also,
    - Reduction in homeostatic pathways involved in:
      - Kidney function (acute renal failure)
      - Maintenance of gastric mucosa (ulcers – diclofenac, aspirin)

COX 2 Selective Inhibitors

- -coxibs are selective for the inducible enzyme isoform – COX-2
- Greater safety with respect to GI adverse effects, less likelihood of GI bleeds
- Cardiovascular effects

CV effects mediated by the balance between TxA2 and PGI2

HMG-CoA Reductase & Statins

e.g. simvastatin

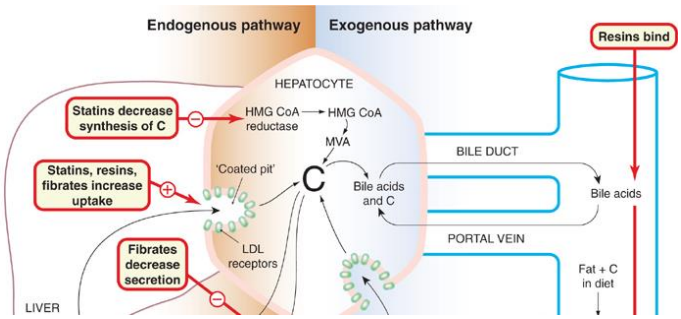


Fig. 24.1 Schematic diagram of cholesterol transport in the tissues, with sites of action of the main drugs affecting lipoprotein metabolism. Atherosclerosis and lipoprotein metabolism. Ritter, James M., DPhil FRCP HonFBPhS FMedSci, Rang & Dale's Pharmacology, 24, 310-318. Accessed via ClinicalKey

Drugs Which Interact With Carrier Proteins

- Examples: Drugs that act on monoamine neurotransmitter uptake proteins
- Fluoxetine (Prozac) – SSRI
- SNRI – initially developed from anti-depressant research; used for weight loss and smoking cessation, e.g. venlafaxine

[Neither of these are on drug lists]
Weight loss = sibutramine (SNRI)
Smoking cessation = buproprione (SDRI; D for dopamine)

Fluoxetine Mechanism

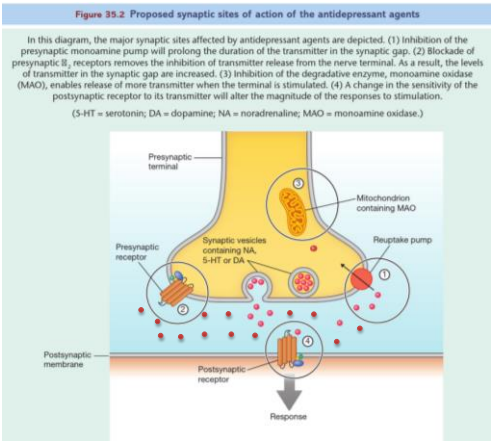
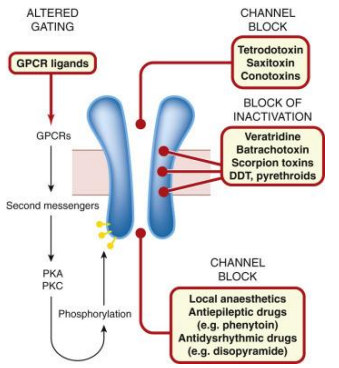


Fig 35.2. Fundamentals of Pharmacology. Bullock S & Manias E. Copyright © 2017, Pearson

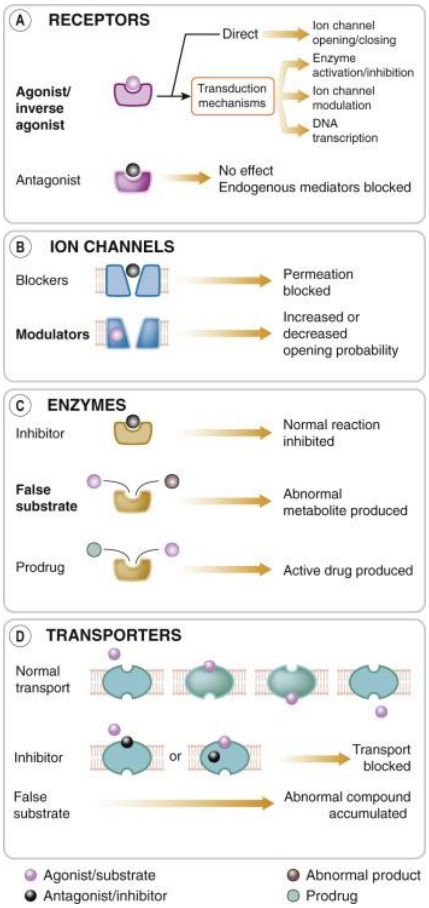
Ion Channels

- Voltage-gated ion channels
  - local anaesthetics (lignocaine),
  - Ca^{2+} channel blockers (verapamil, nifedipine)

Sodium Channels



Drug-binding domains of voltage-gated sodium channels.
How drugs act : molecular aspects.
Rang, HP, MB BS MA DPhil Hon FBPharmacolS FMedSci FRS, Rang & Dale's Pharmacology, 3, 22-49



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