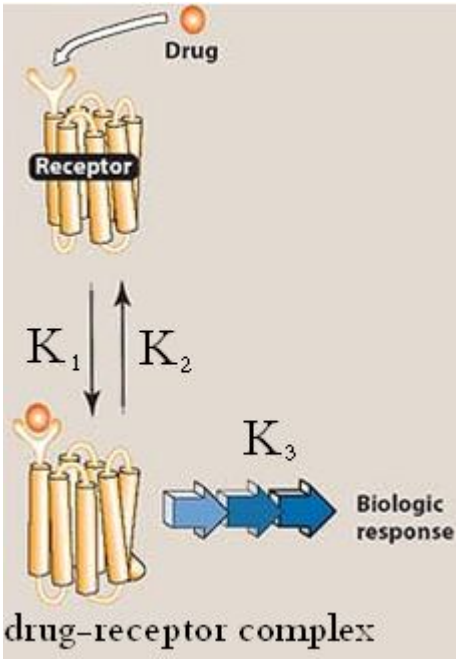
Drug-receptor interactions

Overview

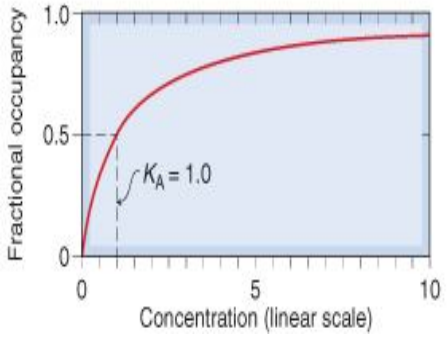


- Most drugs produce their actions by interacting with receptors.
- Drug +receptor ↔ drug-receptor complex → response
- So, a receptor has the ability to bind a drug and then couple this binding to a response. This ability of a receptor makes us expect a response for each drug-receptor complex formed, but in fact, this efficiency of receptors varies and depends on the factors that will be discussed in this chapter.
- *(in the diagram)* ➔ K_1 = association constant
  K_2 = dissociation constant
  K_3 = efficacy
- K_1 and K_2 depend on *affinity* and *occupancy*
  - **Affinity:** ability of a drug to bind to a receptor
  - **Occupancy:** fraction of receptors occupied to the total number of receptors

- **Efficacy:** (intrinsic activity): ability of a drug to change the receptor conformation to produce a response.
- **So,** a pharmacological response depends on the affinity and efficacy.

Drug-receptor binding

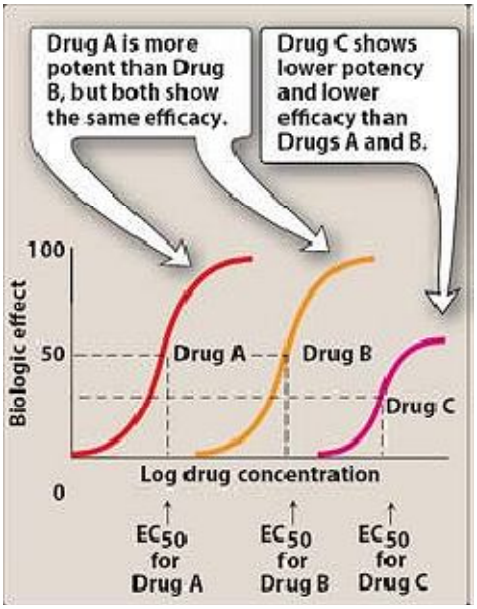
- **Drug + receptor ↔ drug-receptor complex**
  - This equation should follow the law of mass action**,** which means that as the concentration of a drug increases, the number of drug-receptor complex (receptor occupancy) increases.
  - If the affinity increases, then a lower amount of drug will be needed to produce a given occupancy



This curve depends on the affinity only

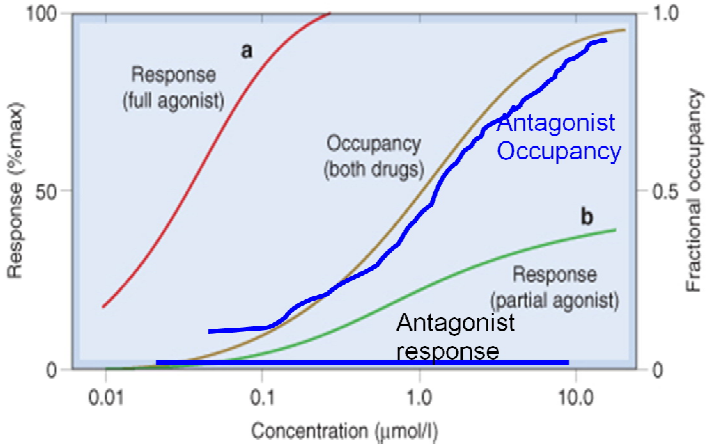
This is a hyperbolic curve

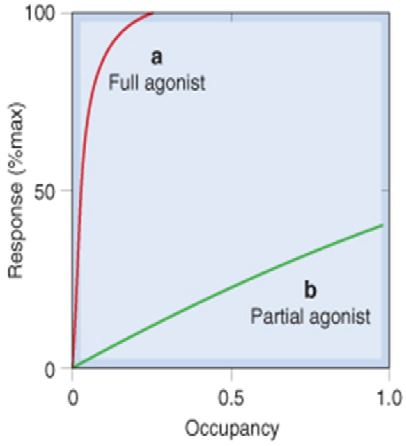
Agonist concentration curves (Dose-response curves)



- We usually use the log of a drug's concentration (instead of using the concentration value itself). This will help us to plot the curve even in extremely low concentrations of drugs.
  - It makes a *sigmoid* (s-shaped) curve *(instead of hyperbolic)*
  - It is called a log-dose response curve (LDR)
- By raising the dose (((above the "threshold dose level"))), there will be a gradual increase in the response of that drug.
- Thus, LDR of similarly active drugs produce parallel LDR curves, enabling us to compare between the potencies of qualitatively similar drugs.
- ***Potency*** (EC_{50} or ED_{50}): the concentration or dose needed to produce a 50% maximal response.
- ***Efficacy*** (E_{max}) is the max response the drug can produce
- Efficacy of an agonist depends on both affinity (binding) & intrinsic activity.
- Concentration-response curves cannot be used for direct estimation of the **affinity** of the agonist to the receptor because:
  - The concentration of the drug at the receptors usually differs from the known concentration
  - Many factors interact produce pharmacologic response or efficacy called "intrinsic activity"
  - *A concentration-occupancy curve is used instead (see above).*

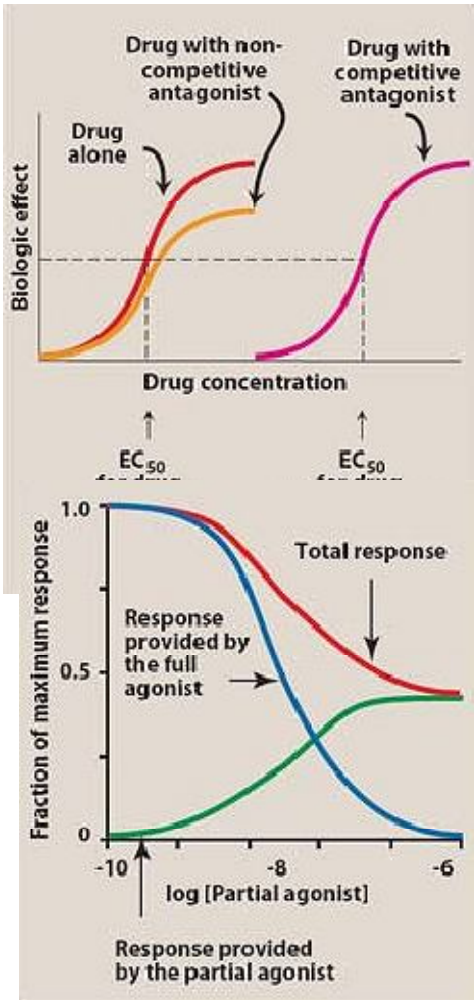
Agonist/Antagonist & Affinity/Efficacy





Difinitions

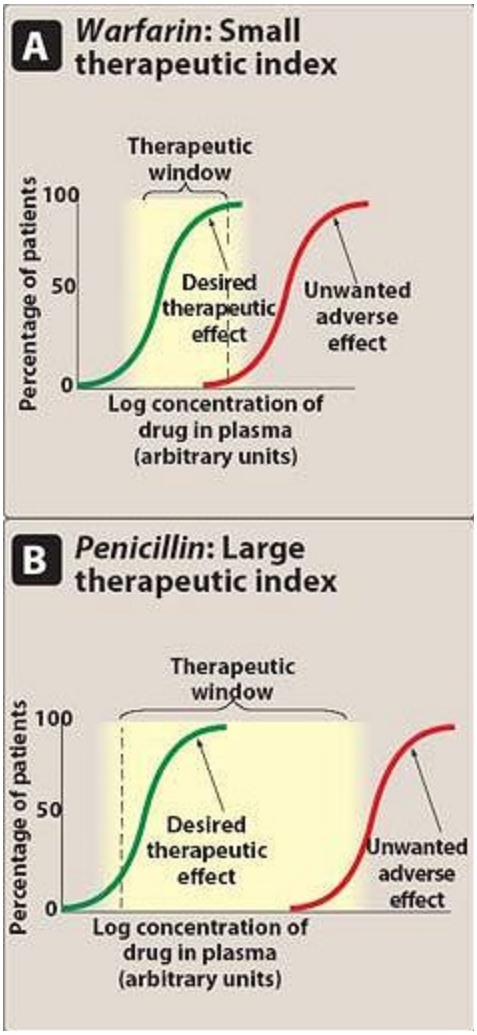
- **Affinity** is the tendency of a drug to bind to its receptor.
- **Intrinsic activity (Efficacy)** is the ability of the drug to activate the receptor.
- ***Full agonist drugs*** have both high affinity and high efficacy .
- ***Partial agonist drugs*** possess weak efficacy even at 100% occupancy, producing only submaximal tissue response
  - ❖ When a partial agonist competes with a full agonist to the receptor, the partial agonist will act as a competiive antagonist, because it will decrease the efficacy of the agonist alone.
- ***Antagonist drugs*** have appreciable receptor affinity but zero efficacies. *(see curve above)*
- ***Inverse agonist***
  - ❖ Some receptors are stable more in active state in absence of endogenous or exogenous agonists
  - ❖ Inverse agonist decreases that constitutive (inherent) activity, keeping the receptor more in the inactive conformation



- **Spare Receptors:**
  - Max drug response can occur at <100% occupancy, i.e., a number of receptors remain unoccupied at 100% effect
  - In D-R interactions, K_d value is higher than EC_{50}, except in the case of presence of spare receptors, where EC_{50} will be higher.

Quantal Dose-Response Curves

- Quantal responses include effects that are either present or NOT
- Examples include vomiting, death, sleeping, toxic effect (bleeding vs no bleeding)
- Most biological responses are graded like blood pressure, plasma cholesterol, body weight,…etc.



Therapeutic Index

- The therapeutic index is the ratio of the toxic or lethal dose of a drug to produce a toxic/lethal effect to the ED_{50} to produce a therapeutic effect
- $TI = LD_{50} / ED_{50}$
- LD_{50} = lethal dose: the concentration of drug that gives lethal effect in 50% of the cases.
- ED_{50} = the concentration of drug that gives a therapeutic effect in 50% of the cases

  !!!!! not the same as ED_{50} in potency !!!!!
- Drugs with high therapeutic index have **wide safety margin**
- Drugs with low therapeutic index have **narrow safety margin**

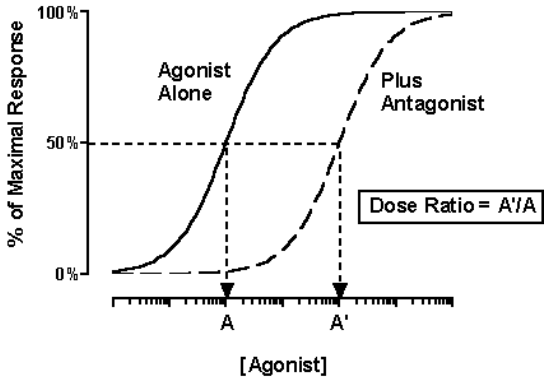
Drug Antagonism

- **Chemical antagonism**, chemicals that disable the drug's effect. *e.g. heparin (negatively charged) is neutralised by positive ionic compounds in the blood.*
- **Pharmacokinetic antagonism**, by enhancing hepatic metabolism of the drug by another (warfarin and barbiturates), or gastrointestinal absorption inhibition.

- **Physiologic antagonism:** counteracting the action of a drug functionally
- **Receptor blockade antagonism**

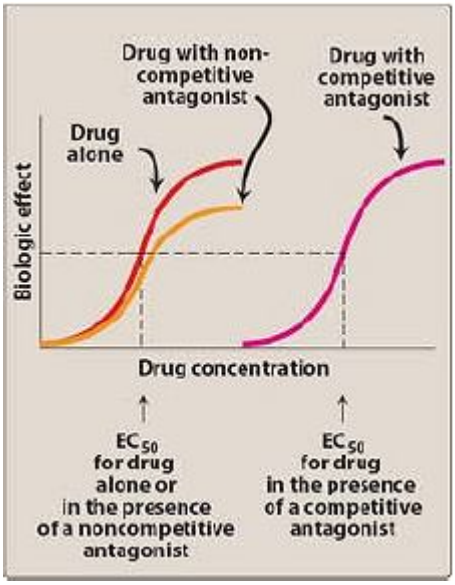
Reversible (Surmountable) Competitive Antagonism

- An antagonist drug binds selectively & prevents the agonist binding
- Increasing agonist concentration can restore the agonist occupancy (surmountable))
- They increase the ED50 of the agonist, but **not Emax or the slope**
- Most antagonistic drugs are competitive



Irreversible Competitive Antagonism

- **Antagonist molecule** dissociates very slowly or not at all from the receptor-antagonist complex.
- Increasing the agonist **does not effect antagonist occupancy or the receptor blockade (non-surmountable blockade).**



Non competitive antagonism

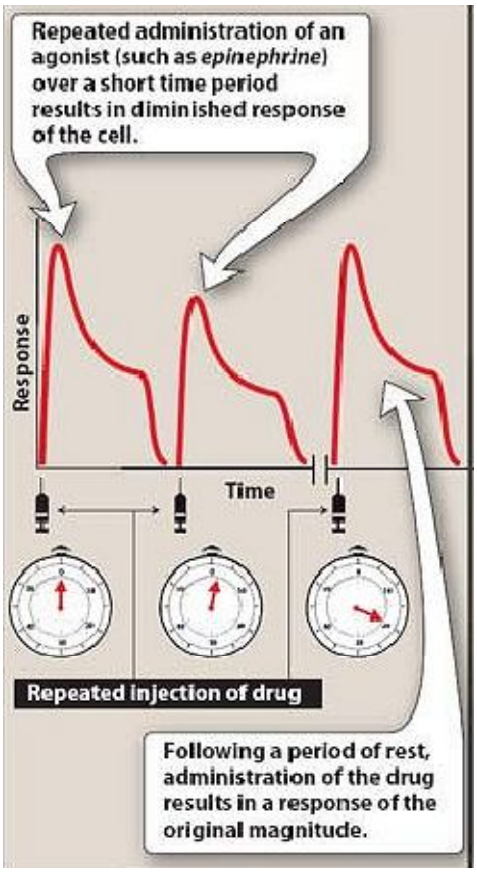
- Antagonist bind to other site than the active site (**doesn't effect the binding between the receptor and the agonist).**
- They may block any point in the transduction cascade.
- They cause ↓in the slope and ↓of the Emax
- No effect on EC50

Desensitization and Tachyphylaxis

- **Tachyphylaxis** the rapid diminishing response of a drug after a drug's administration.
- Receptors are said to be desensitized
- **Desensitization and tachyphylaxis** are used when it is developing in the course of few minutes.
- ***Tolerance*** describes a more gradual loss of drug-induced clinical effects that develop in the course of days or weeks.
- **Refractoriness** is sometimes used to indicate the loss of therapeutic response.
- ***Drug resistance*** describes the loss of the effect of anti-tumour and antimicrobial drugs.

Mechanisms of Desensitization

1. Conformational change in receptors or receptor phosphorylation
2. Down-regulation of receptors
3. Depletion of mediators
4. Pharmacokinetic desensitization
5. Pumping of drugs out from intracellular site (chemotherapy)



1- Receptor Changes

- **Conformational change** in the receptor that the agonist-receptor binding occurs but the transduction (activation) does not take place,
- **Phosphorylation of the intracellular regions of the receptor protein** interferes with its ability to activate target channels or enzymes producing second messengers

2- Receptor down-regulation

- This process usually takes place with prolonged exposure to agonist drugs leading to **a gradual decrease in the number of receptors** expressed on cell membrane
- Receptor down-regulation is a slower process than receptor-second messenger uncoupling

3- Depletion of Mediators

- Drugs acting indirectly via transmitter release can cause depletion of that transmitter and hence loss of action

4- Pharmacokinetic Desensitization

- Drugs which stimulate hepatic metabolism may enhance their own metabolism and hence a lower plasma concentration with repeated administration of the same dose

Self-Assessment Questions

- ✓ What are the main molecular targets for Drugs? Can you consider plasma membrane and cell organelles as molecular targets?
- ✓ Describe the structure of each of the four main classes of receptors.
- ✓ Mention the changes that occurs upon binding of an agonist to each of the four main classes of receptors.
- ✓ Mention different mechanisms of receptor desensitization.
- ✓ Define full agonist, partial agonist, antagonist as regards: affinity (binding, occupancy), efficacy & intrinsic activity
- ✓ Describe the effects of competitive, non-competitive antagonists on agonist D-R curve
- ✓ Drug A has almost equal K_d values for receptor X_1 & X_2 subclasses, whereas drug B K_d value for X_1 is much lower than that for X_2 receptor subtype. Make a conclusion about the specificity of the given drugs for the receptor subtypes. Are A & B agonists or antagonists or can be either?