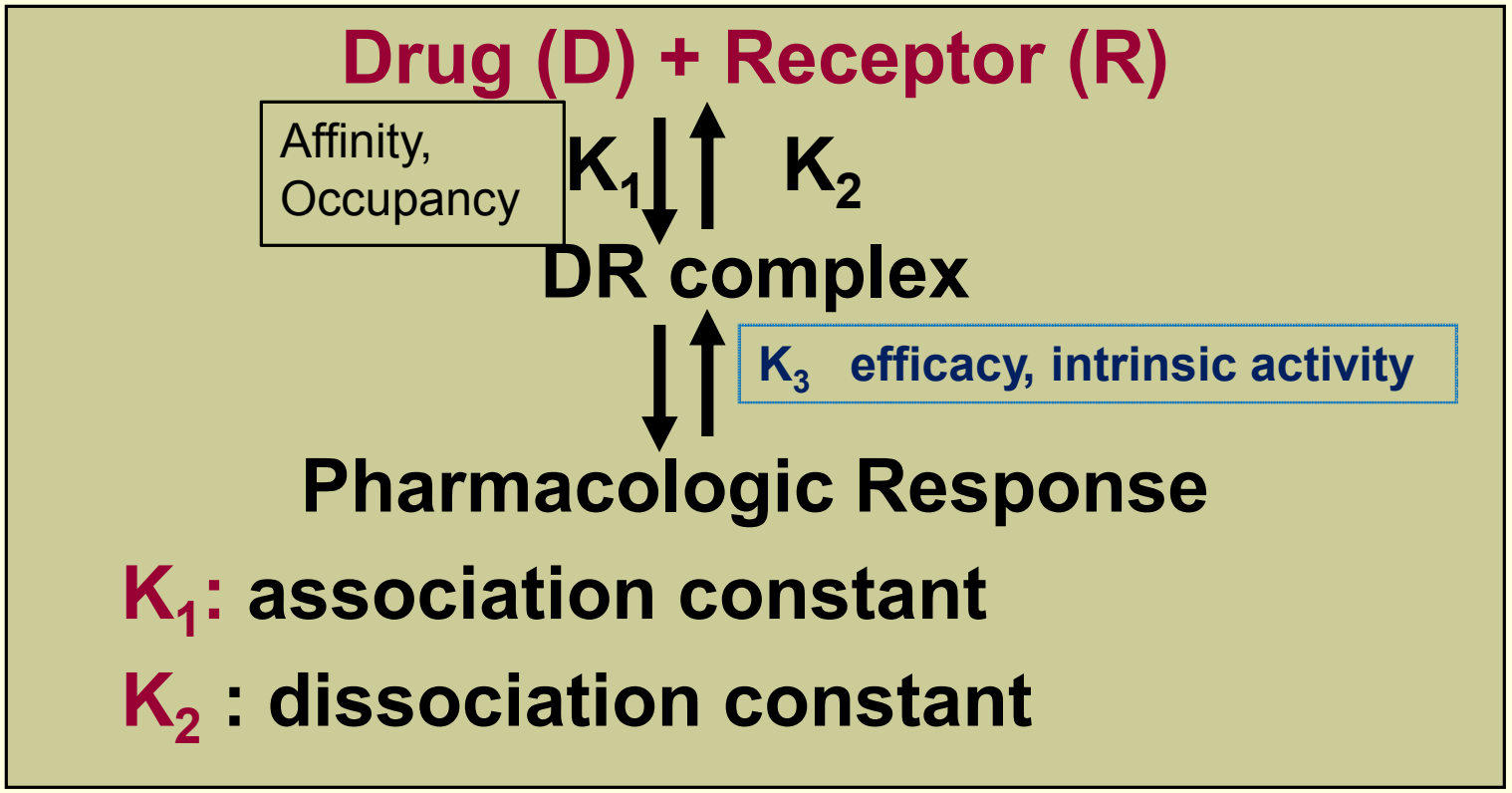
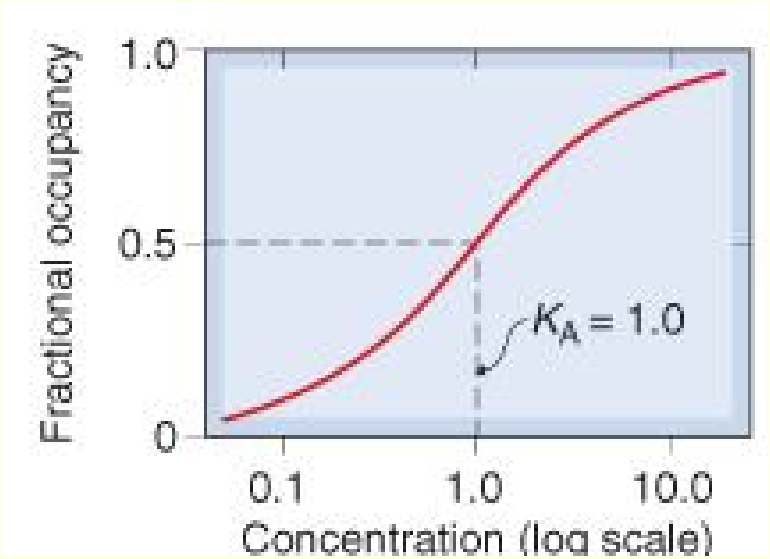
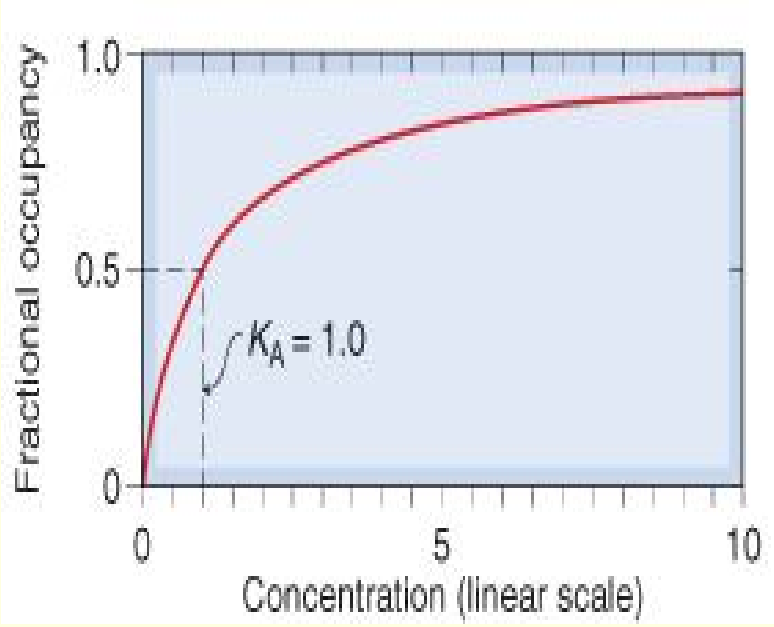
DRUG-RECEPTOR INTERACTIONS



Drug- Receptor Binding

- Drugs binding to receptors follows the Law of Mass Action
- At equilibrium: Receptor Occupancy α Drug Concentration
- The higher affinity, the lower the concentration producing a given occupancy
- Fractional occupancy= D-R complex/total No of receptors
- Lower Kd means higher affinity or binding to the receptor



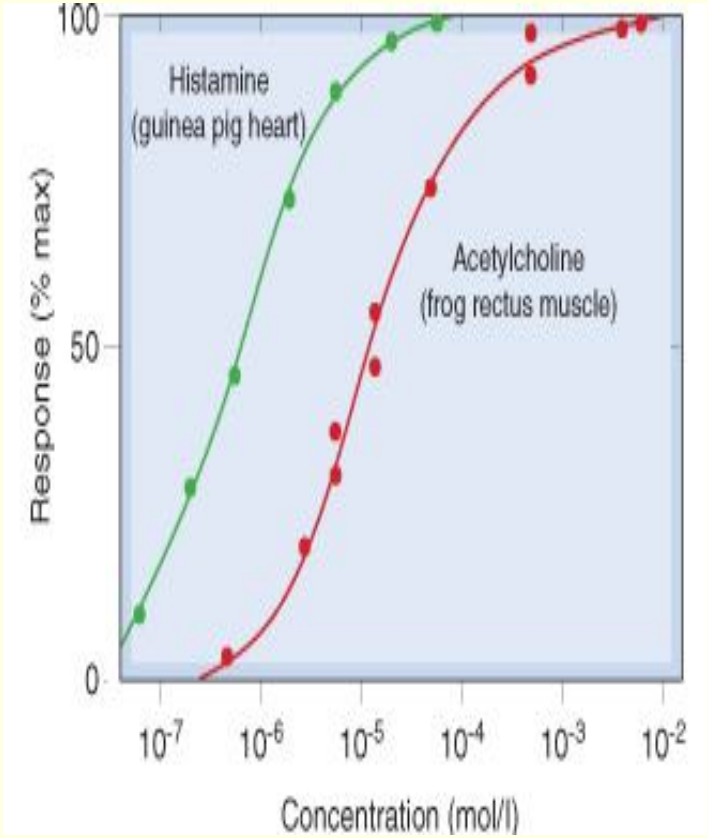


DRUG- RECEPTOR BINDING

- D + R $\rightleftharpoons$ DR complex
- According to the law of mass action: the relationship between the free (R) and bound receptors (DR) is described:
- K_d = [D] [R]/ [DR] K_A: [DR] / [D] [R]
- K_d is constant and intrinsic property for any given receptor-drug pair
- $K_{d(A)}$; dissociation constant is the concentration of the ligand at which 50% of the available receptors are occupied

Agonist Concentration-Effect Curves

- **Plotting pharmacologic response versus log concentration produces *S-shaped or "sigmoidal" graded* log *concentration-effect* or log *dose-response curve (LDR)***

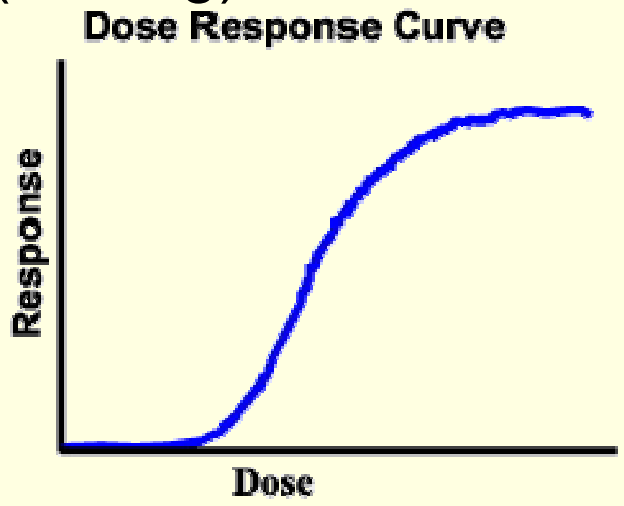


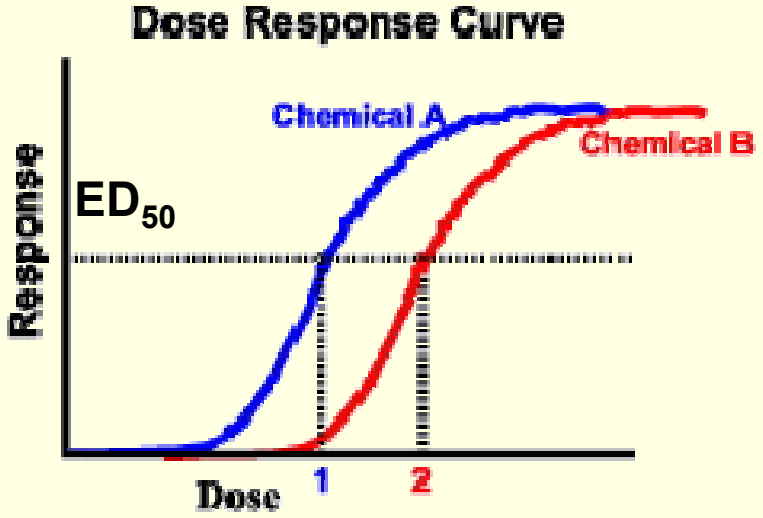
Dose-Response Curves

- By raising the dose above the "threshold dose level", a gradual increase in response occurs
- Thus, LDR of similarly active drugs produce parallel LDR curves, enabling us to compare between the potencies of qualitatively similar drugs
- Affinity is a term used to describe the ability of a chemical to bind to a receptor or molecular target (occupancy)

Dose-Response Curves

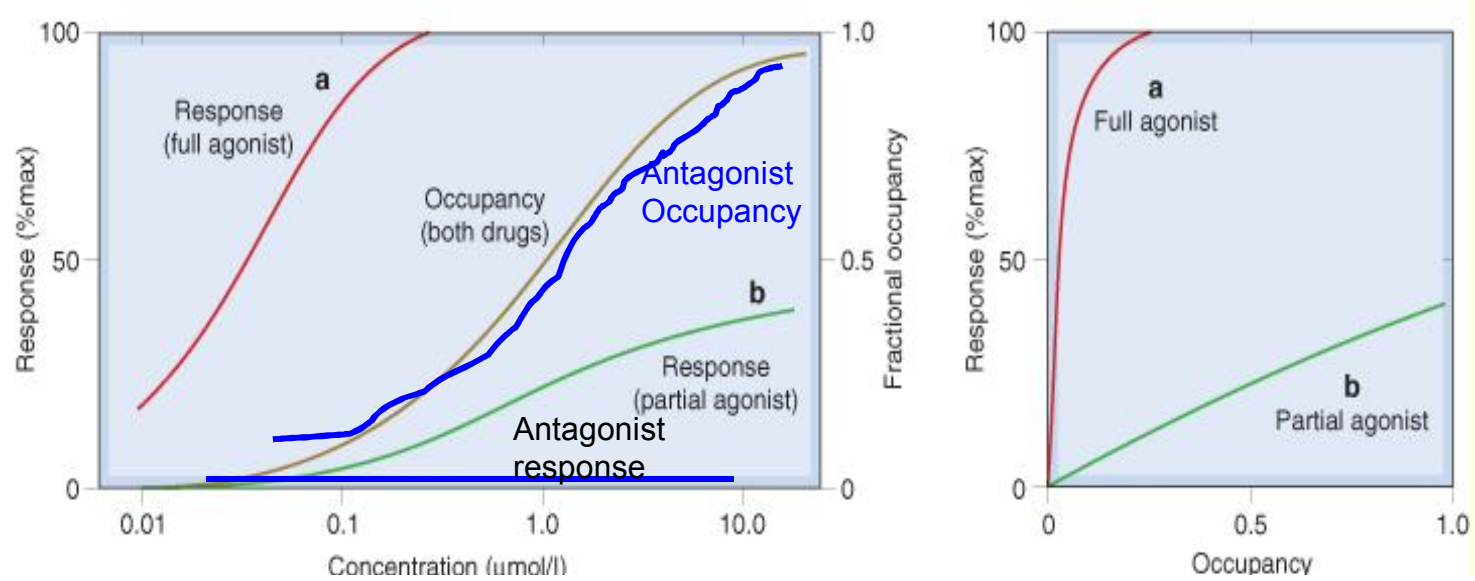
- ***Potency*** **presented as the concentration or dose needed to produce a 50% maximal response (EC_{50} or ED_{50})**
- ***Efficacy*** **(max response) is the max response the drug can produce (E_{max})**
- Efficacy of an agonist depends on both affinity (binding) & intrinsic activity





Dose-Response Curves

- **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"**



Agonist/Antagonist & Affinity/Efficacy

- ***Affinity*** is the tendency of a drug to bind to its receptors
- 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 only weak efficacy even at 100% occupancy, producing only submaximal tissue response
- *Antagonist drugs* have appreciable receptor affinity but zero efficacies
- Partial agonist functions as compet. antagonist in presence of the full agonist (mixed agonist-antagonist)

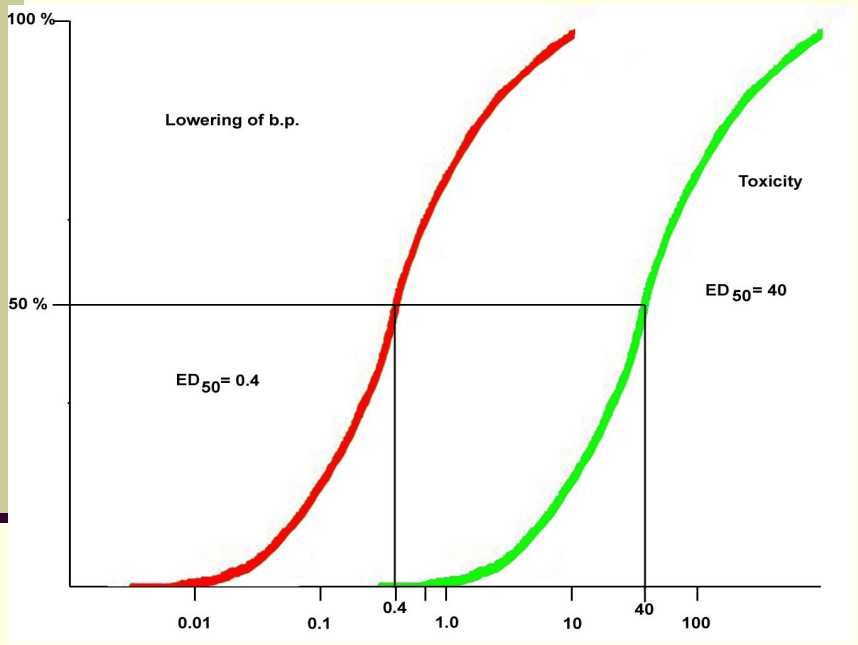
Inverse Agonists & Spare Receptors

- ***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 most D-R interactions, K_d value is higher than EC_{50}
  - *Draw a curve representing the above fact.*

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



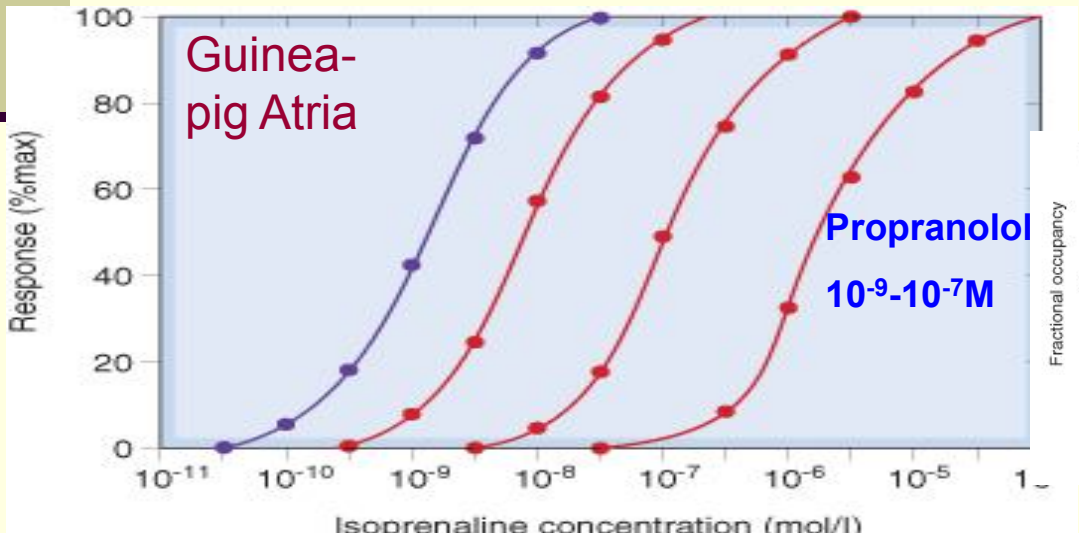
- The therapeutic index is the ratio of the toxic or lethal dose of a drug to produce a toxic/lethal effect to the ED_{50} to produce a therapeutic effect
- $TI = LD_{50}/ED_{50}$
- Drugs with high therapeutic index have wide safety margin like penicillin
- Drugs with low therapeutic index have narrow safety margin like warfarin & digoxin

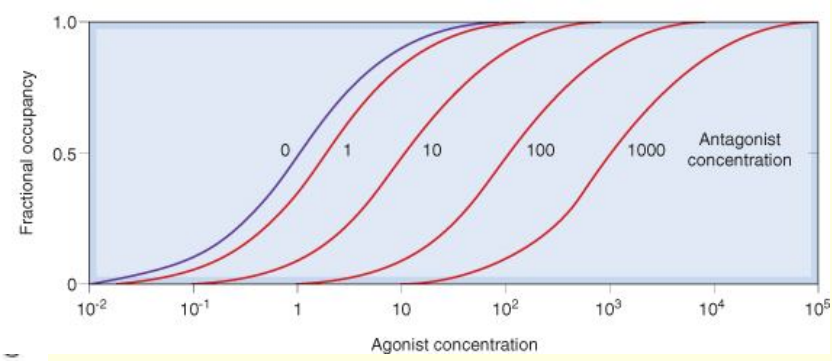
Drug Antagonism

- **Chemical antagonism**, for example neutralization of protein mediators like inflammatory cytokines with antibodies
- **Pharmacokinetic antagonism**, by enhancing hepatic metabolism of the drug by another (warfarin and barbiturates), or gastrointestinal absorption inhibition
- **Physiologic antagonism**
- **Receptor blockade antagonism**

Reversible (Surmountable) Competitive Antagonism

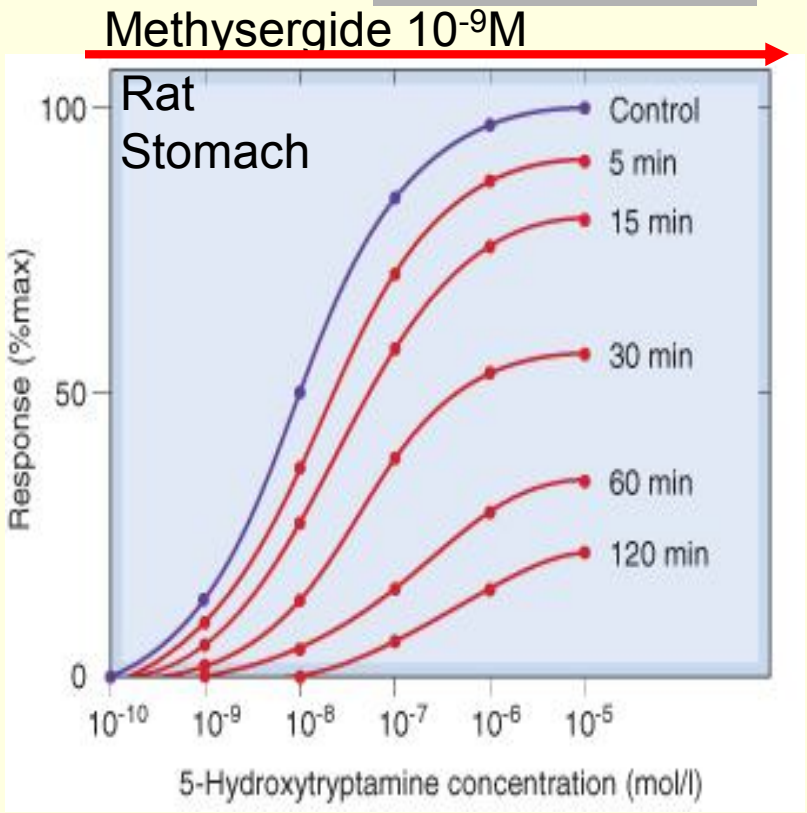
- ***An antagonist drug binds selectively & prevents the agonist binding***
- **Increasing agonist concentration can restore the agonist occupancy and hence the response**
- **They increase the ED_{50} of the agonist, but *not E_{max} or the slope***
- **Most antagonistic drugs are competitive**





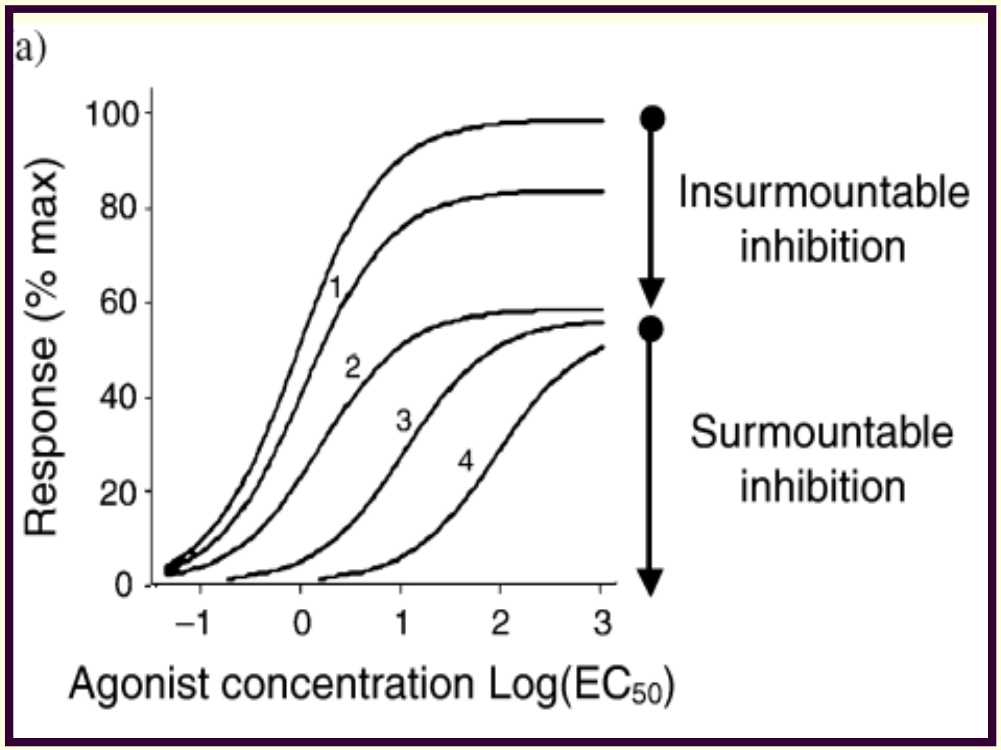
Irreversible Competitive Antagonism

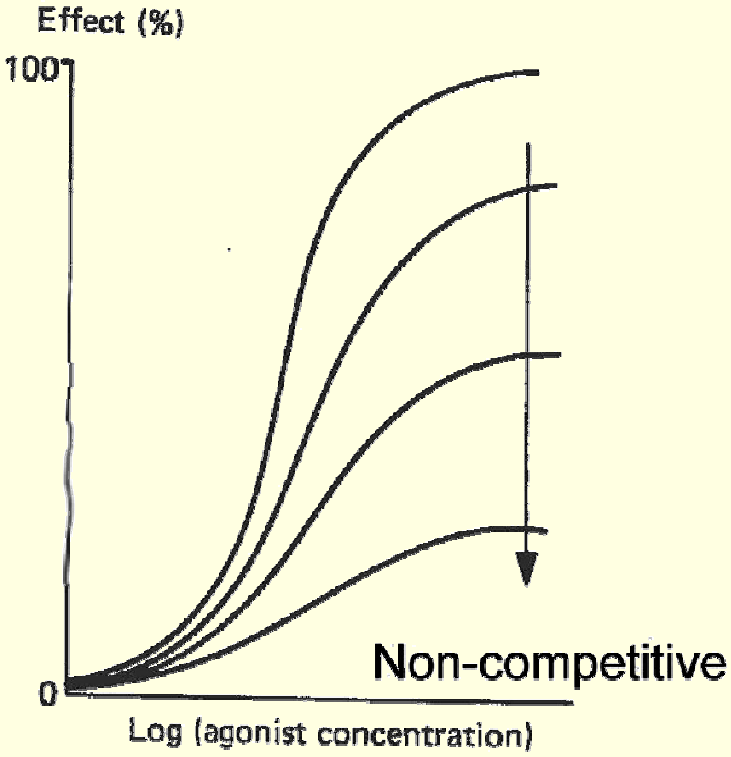
- **Antagonist molecule *dissociates very slowly or not at all from the receptor-antagonist complex***
- **Increasing the agonist *does not affect antagonist occupancy or the receptor blockade* (non-surmountable blockade)**
- **Aspirin is an irreversible antagonist of COX enzyme of platelets**



Non-competitive antagonism

- Antagonists do NOT affect the agonist receptor binding
- They block at a point the chain of transduction cascade
- They cause a reduction of the slope & the max of the agonist concentration-response curve
- No effect on agonist ED_{50}
- Example: Ca^{2+}-channel antagonists block the entrance of Ca^{2+} via voltage-operated Ca^{2+} channels





Non-competitive blockers change the efficacy of the drug but not its potency

Desensitization and Tachyphylaxis

- ***Tachyphylaxis** is the loss of drug effect when applied to the tissue frequently at short time intervals*
- ***Receptors are said to be desensitized***
- ***Desensitization and tachyphylaxis** are used when it is developing in the course of few minutes*

Desensitization and Tachyphylaxis

- ***Tolerance*** **to describe a more gradual loss of drug-induced clinical effects that develops 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**

Mechaniasms of Desensitization

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

1- Receptors Changes

- ***Conformational change*** **in the receptor that the agonist-receptor binding occurs but the transduction (activation) does not take place,**
- **Example: desensitization of cholinergic ionotropic receptors at the neuromuscular junction**
- ***Phosphorylation of the intracellular regions of the receptor protein*** **interferes with its ability to activate target channels or enzymes producing second messengers**
- **Example: desensitization of β-adrenoceptors**

2- Receptor downregulation

- **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
- Tachyphylaxis to the effects of amphetamine or ephedrine, acting by releasing catecholamines from nerve terminals is an example

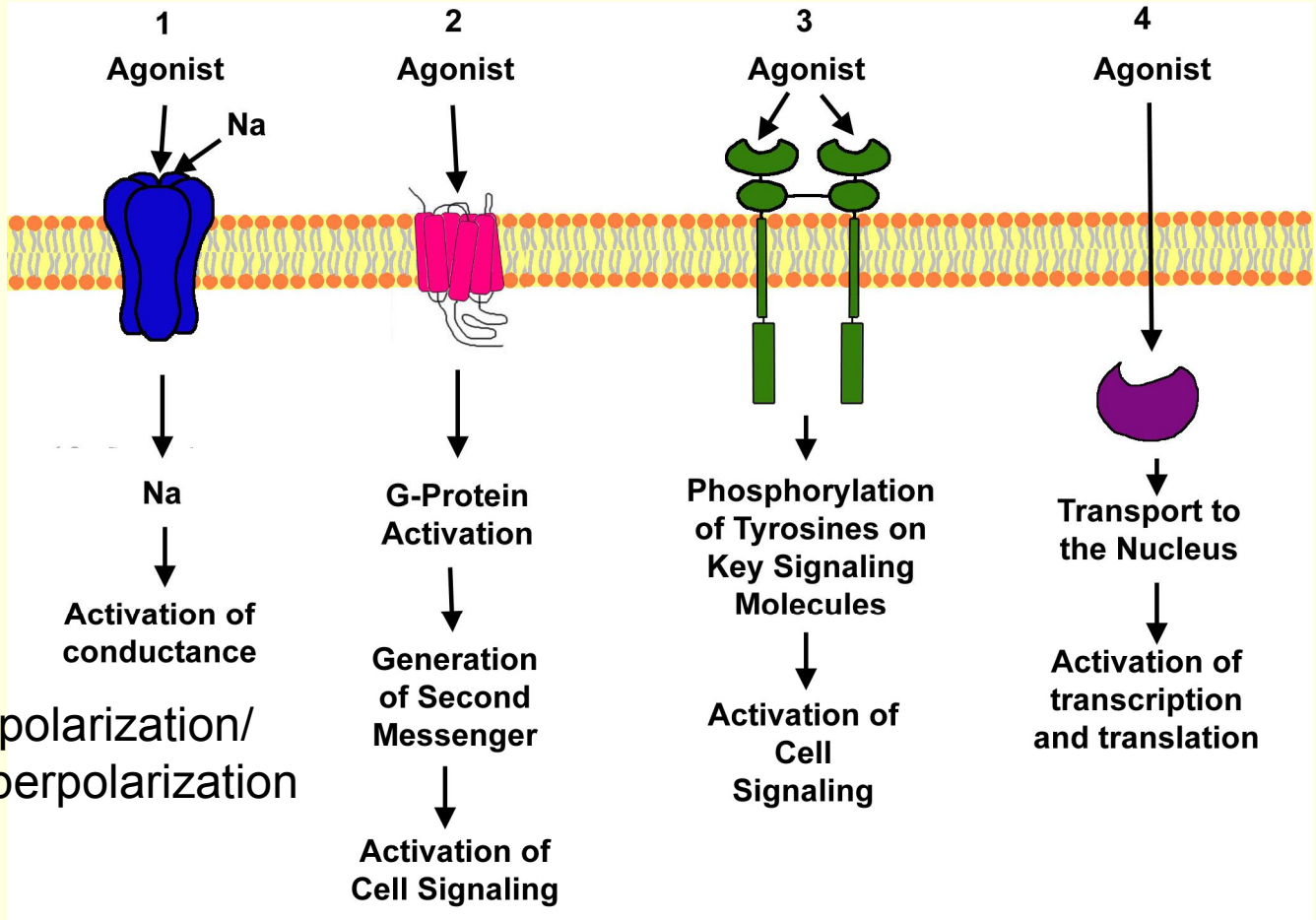
4- Pharmacokinetic Desensitization

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

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.

Consequences of Agonist-Receptor Binding



Depolarization/ hyperpolarization

Self-Assessment Questions (Continue)

- 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?