Pharmacodynamics

Means mechanism of action (MOA)

Drugs could either act through receptor or non-receptor mechanisms

1. <u>Non-receptor mechanisms:</u>

a. Physicochemical mechanisms:

- Osmotic diuretics   Urea; Mnnitol

- Osmotic cathartics   Lactulose

- Neutralizing effects   Antacids

- Detergent effect   Disinfectants; Oxidizing agents

- ↓ excitability of membranes (stabilize cell membranes)   Local anaesthetics

b. Interaction of drug with small molecules or ions:

- EDTA binds Pb^{++} with high affinity → ↑ exc.

Penicillamine binds $Cu^{++} \rightarrow \uparrow$ exc.

Dimercaprol (PAL); chelates arsenic, mercury, gold, bismuth

c. Incorporation of drug into macromolecules:

Antimetabolites e.g. 5-bromouracil is similar in its structure to thymine (replaces thymine during DNA synthesis $\rightarrow \uparrow$ chromosomal breakage $\rightarrow \uparrow$ anticancerous effect)

5-fluorouracil replaces uracil during RNA synthesis → faulty protein synthesis

Ethionine replaces the a.a methionine → faulty protein

d. Enzyme inhibition (some consider enzymes being receptors to drugs):

Cyclooxygenase inhibitors   NSAID's

Cholinesterase inhibitors   Neostigmine

Decarboxylase inhibitors   Carbidopa

Bacterial dihydrofolate reductase inhibitor Trimethoprim...etc

2. Receptor-mediated effects:

$$D + R \rightleftharpoons DR \text{ complex} \longrightarrow \text{response}$$

Receptor: macromolecule or the component of a cell or organism that interacts with a drug and initiates the chain of biochemical events leading to the drug's observed effects

Receptors

- Found in target cells or tissues

- Determine the dose or concentration of drug required to form a significant no. of drug-receptor complexes

- No. of receptors may limit maximal effect a drug may produce

- Mediate effects of agonists and antagonists

- Responsible for selectivity of drug action

■ Size, shape, electrical charge of drug determines binding to a receptor

■ Changes in a drug's chemical structure can alter the affinity for the receptor where therapeutic and toxic effects may be altered

(a) **Hormones** are secreted by endocrine glands or cells into the blood. Only target cells with receptors for the hormone will respond to the signal.
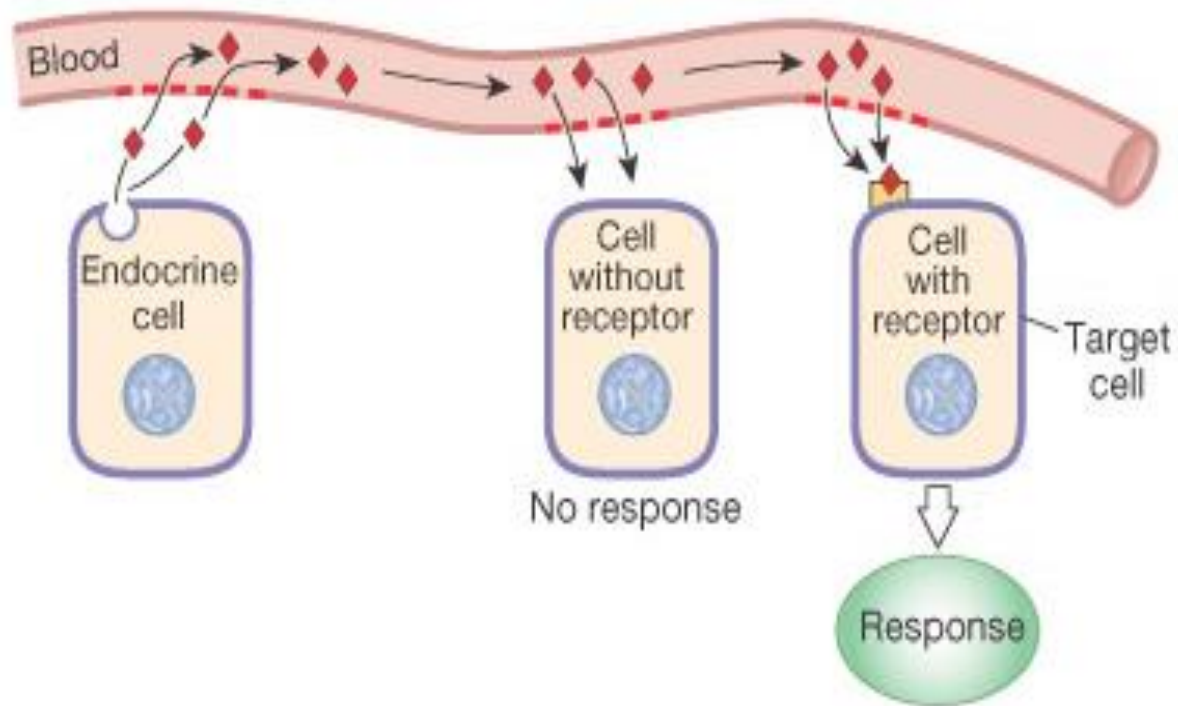
Rational Drug Design

- Drugs are designed based on the structure of the receptor site

- Computers help us do this (match drug to receptor site to increase selectivity)

Lock and key theory

Binding of D to R requires that:

- Both D and R should be close enough to each others

- The R has to be complementary in it's chemical structure to the D

- Binding of the D to the R should be reversible

The interaction of D with R depends on:

- Chemical structure of D and R

- Sites of loss

    e.g. proteins (plasma albumin); nucleic acids; melanin; glycosaminoglycans...etc)

- Intermolecular binding forces

Binding forces between D & R:

- Van der Waals:

The weakest bond   —N…..N—

The commonest (most universal) bond between the D & R

Close approximation between the D & R is required

The R chemical structure should be complementary to the D

- Hydrogen bond:

Stronger than Van der Waals

Reversible

Occurs when a hydrogen connects 2 oxygens or 2 nitrogens

$$-O\ H......O=$$
$$-N\ H......N=$$

- Ionic bond:

Stronger than hydrogen bond

Reversible

Occurs between ions of different charges

$$Na^+ - ..... - Cl^-$$

- Covalent bond:

Irreversible bond

The least common bond between the D & its receptor

The strongest bond; energy is required to break it down

Occurs when the D and the R share a pair of electrons

Three aspects of drug-receptor function:

1. Receptors determine the quantitative relation between drug concentration and response

- This is based on receptor's affinity to bind and it's abundance in target cells or tissues

- Drug response depends on:

    - Affinity of drug for receptor

    - Drug's efficacy (degree to which a drug is able to induce maximal effects)

2. Receptors (as complex molecules) function as regulatory proteins and components of chemical signaling mechanisms that provide targets for important drugs

3. Receptors determine the therapeutic and toxic effects of drugs in patients

Major receptor families:

- Ligand-gated ion channels

- G protein-coupled receptors

- Enzyme (tyrosine kinase)-linked receptors

- Intracellular receptors (ligand-activated transcription factors)

Ligand-gated ion channels

- Responsible for regulation of the flow of ions through channels across cell membranes

- Regulated by binding of a ligand to the channels

e.g. the nicotinic receptors, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle

G protein-coupled receptors

Receptors on the inner face of the plasma membrane regulate or facilitate effector proteins through a group of guanosine triphosphate (GTP) proteins known as G proteins (transmembrane proteins)

e.g. Some hormones peptide receptors and neurotransmitter receptors (e.g., adrenergic and muscarinic receptors) depend on the G proteins that mediate their action on cells

Enzyme-linked receptors

- Binding of the ligand to the extra cellular domain activates or inhibits the related cytosolic enzyme

- The most common are the receptors that have a tyrosine kinase activity as part of their structure, in which the binding results in phosphorylation of tyrosine residues of specific protein

- The addition of phosphate group can modify the three-dimensional structure of the target protein, and so resulting in molecular switch (cellular effect)

Intracellular receptors

- In this family the ligand must diffuse into the cell to interact with the receptors

- The ligand must have sufficient lipid solubilities to be able to move across the target cell membranes

- The best example being the steroids hormones. In which the activated ligand-receptor complex migrate to the nucleus, where it binds to a specific DNA sequences, resulting in regulation of the gene expression
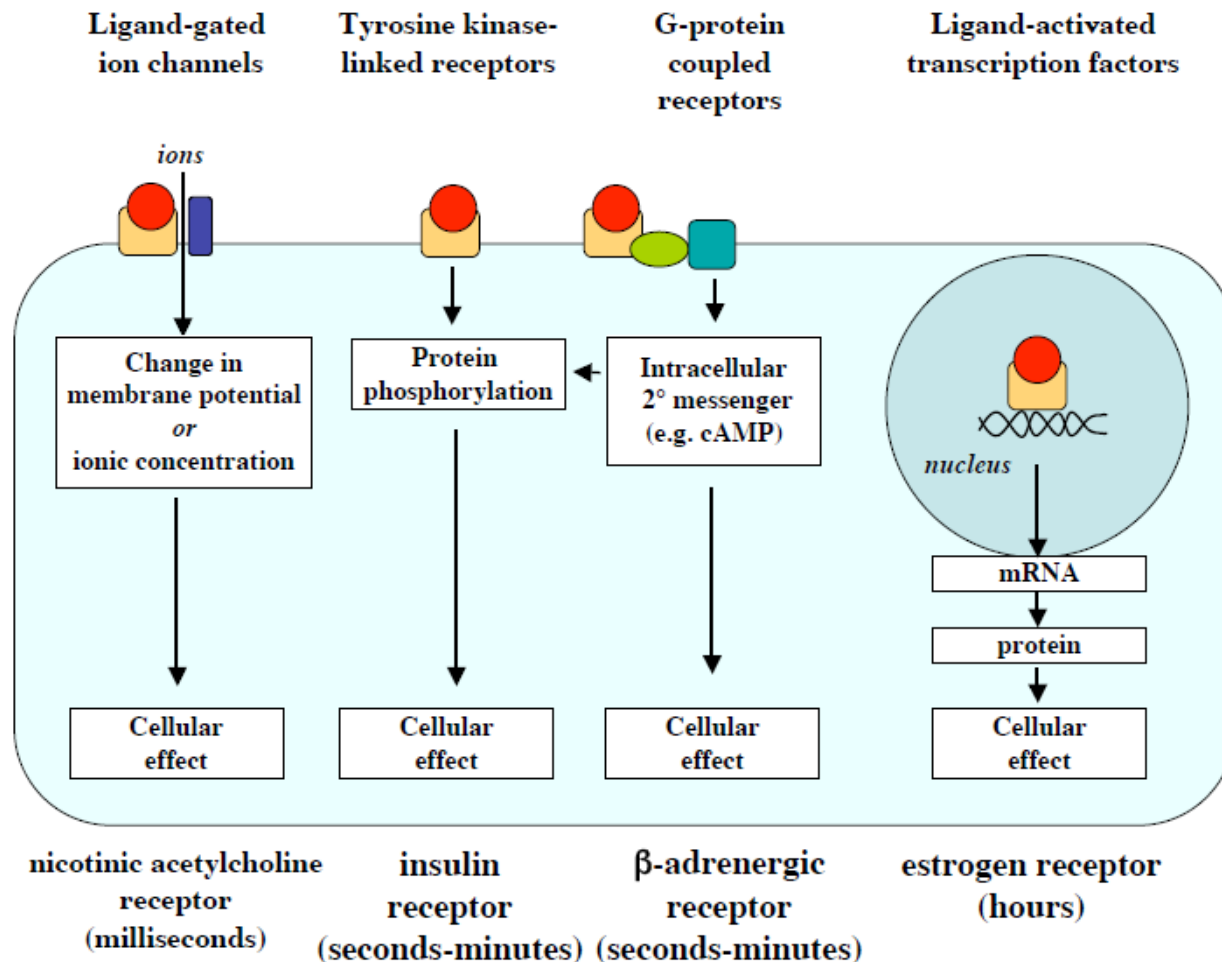
2nd messenger concept
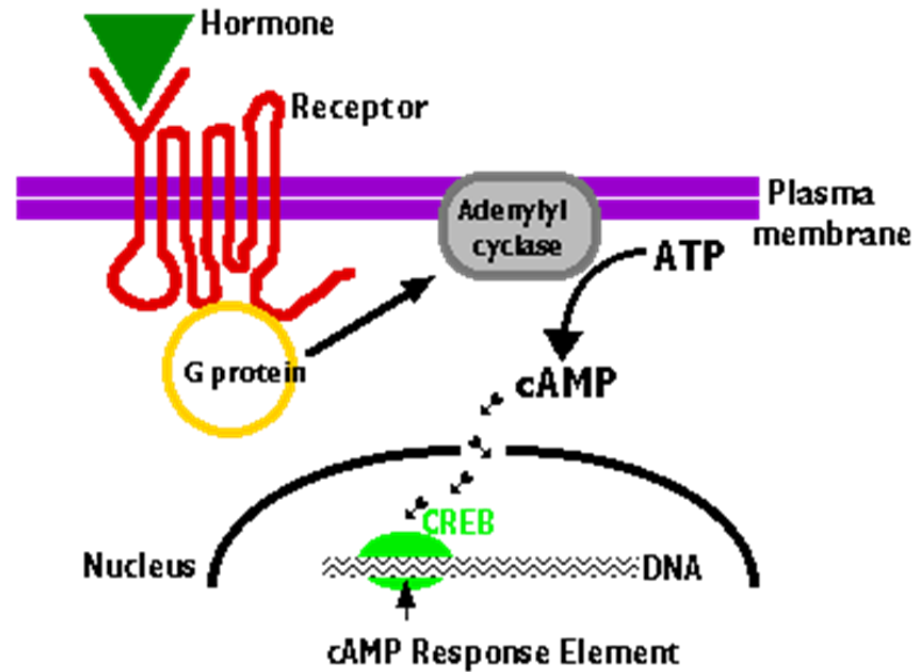
2nd messengers involved in mediating effects of different drugs include:

cAMP;

cGMP;

DAG;

Ca^{++} ;

ITP (IP_3)...

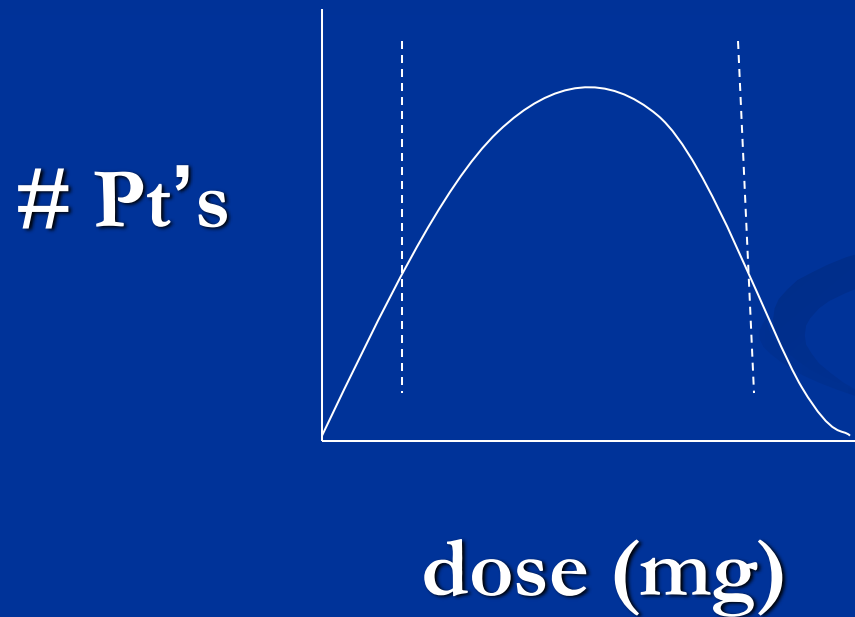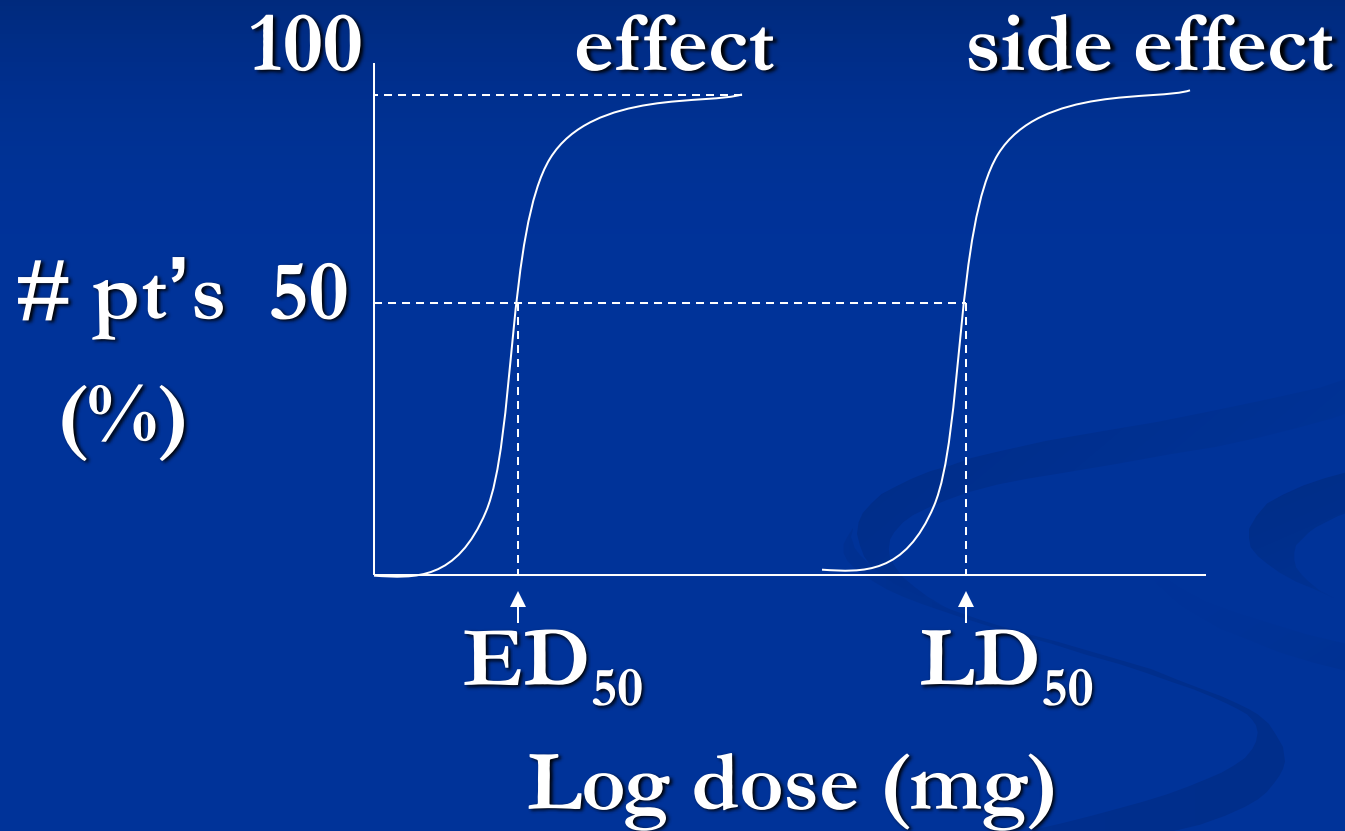# Quantitative studies of drug action

Dose response curves:

- Graded dose-response curves
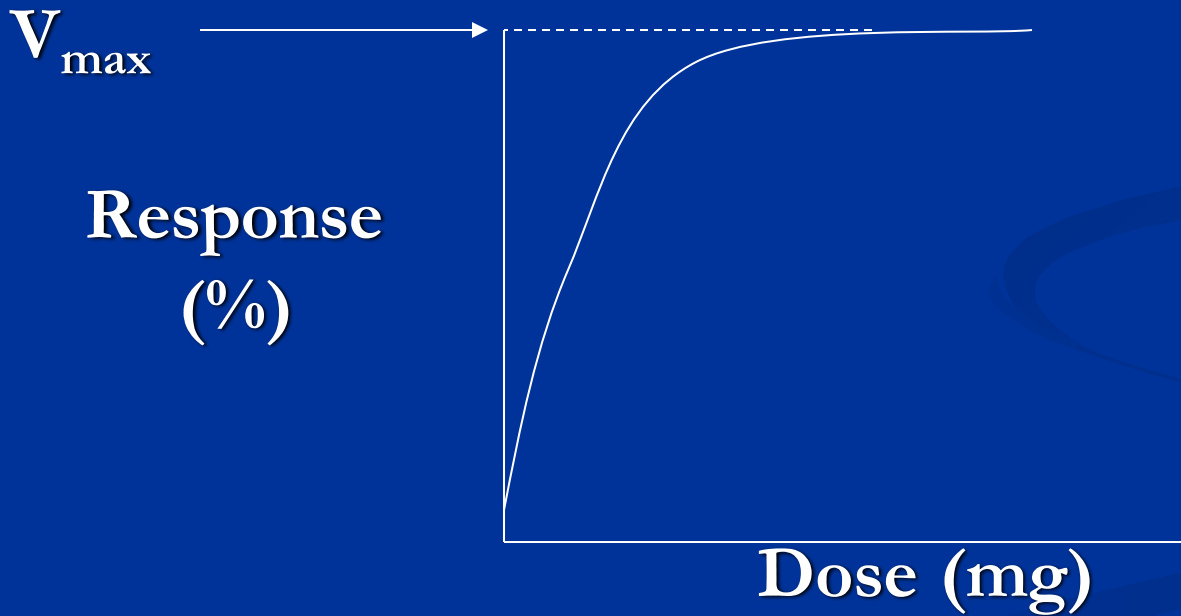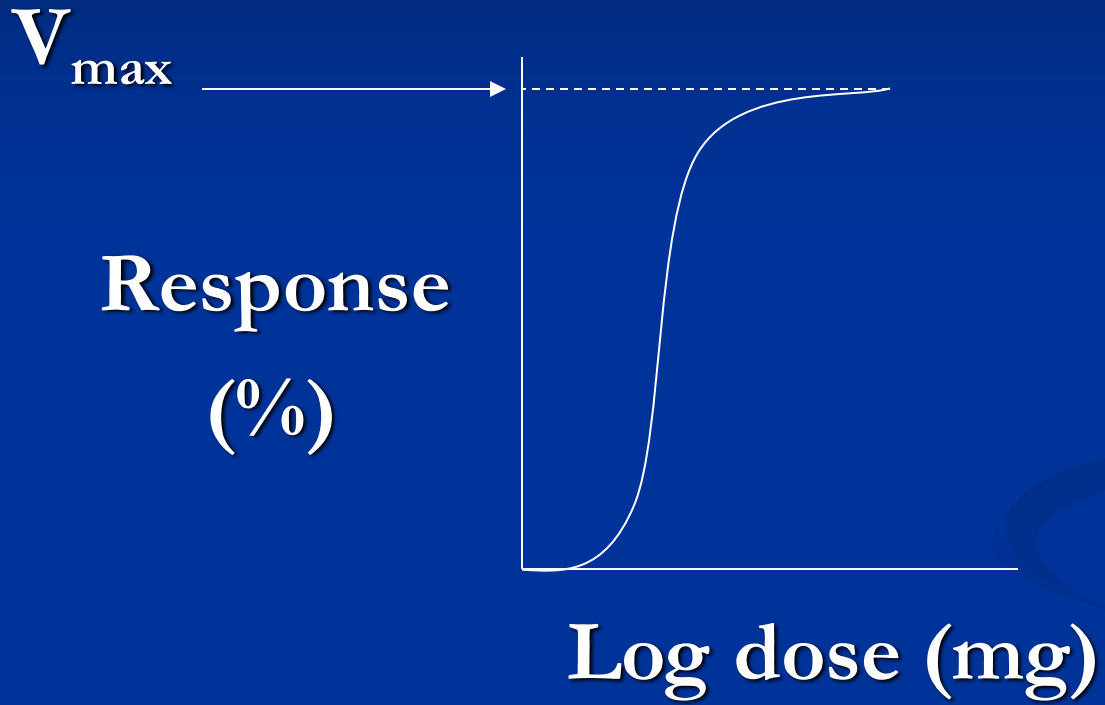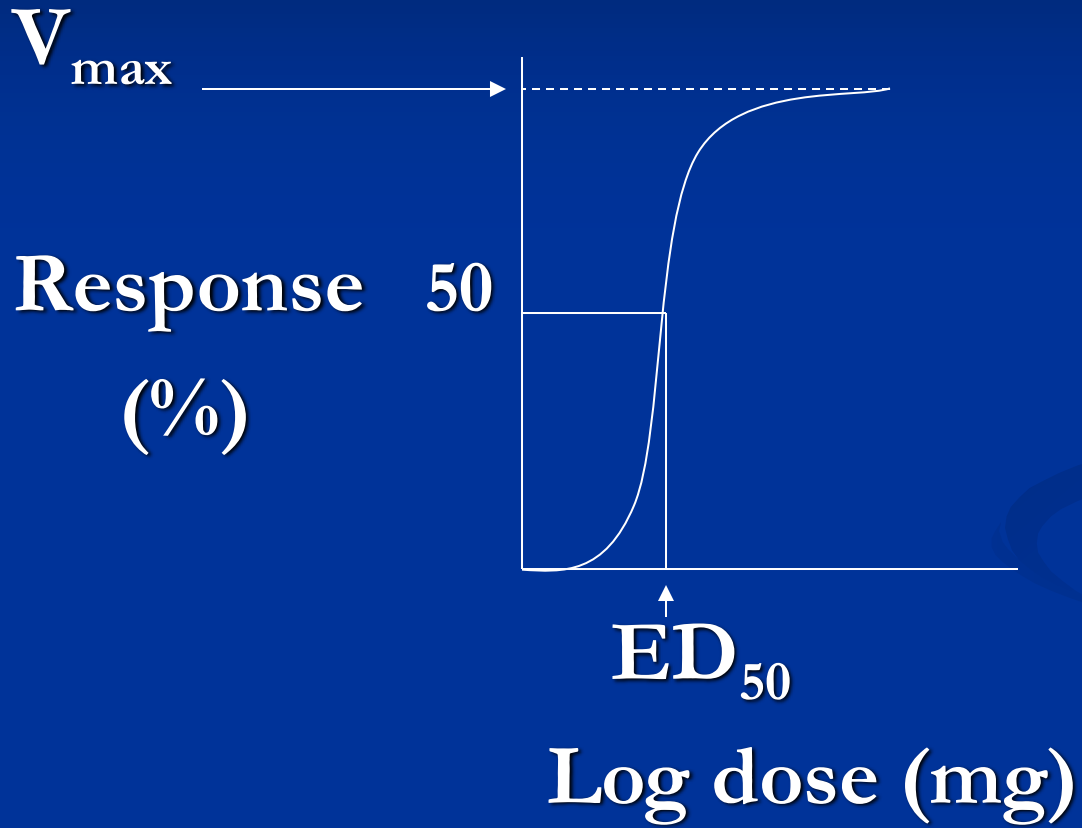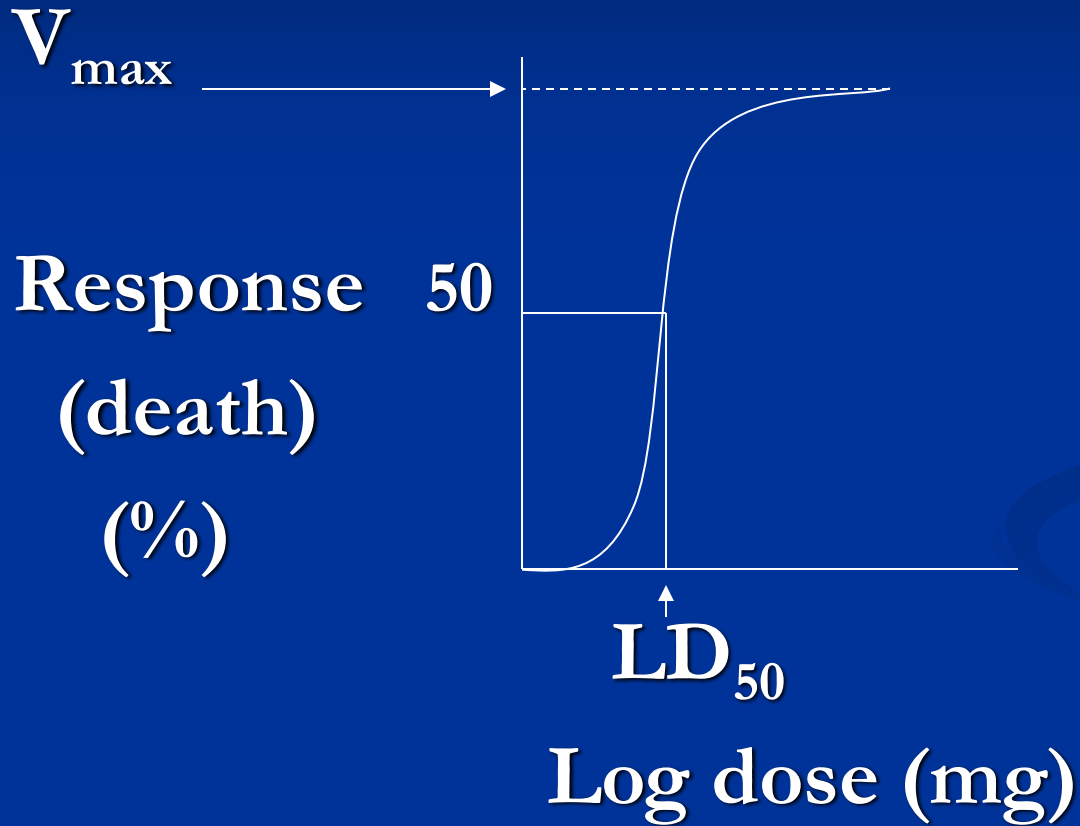
- V_{max}:

Maximum response. Also known as efficacy or intrinsic activity. It is important in pharmacology

- ED_{50}:

The dose which produces 50% of response

- LD_{50}:

The dose which produces death in 50% of animals

* Death is considered the most severe side effect to any drug

- Therapeutic index (TI):

A measure of the safety of drugs

$$TI = LD_{50}/ED_{50}$$

The larger the TI the more safe is the drug

- Potency:

A term used whenever we compare the activity of two drugs producing the same effect

Defined as the dose of one drug necessary to produce a specific response as compared to a second drug producing the same effect

- Affinity:

The ability of a drug to form a stable complex with the receptor

■ **Evaluation of drug safety:**

1. Therapeutic index (TI) (LD50/ED50)

2. Margin of safety (LD0.1/ED99.9) (should be more than 1)

A ratio of more than 1 means that the given dose is effective in > 99% of people and producing death or side effects in < 1% of people

Margin of safety= $\dfrac{\text{LD1 - ED99}}{\text{(ED99)}}$ x 100%

For example, if a 100mg of drug causes toxicity in 1% of the population and 10mg is effective in 99 %, then the standard margin of safety equals to:

$$\dfrac{100 - 10 \text{ x } 100 = 900}{10}$$

This means that the dose which is effective in 99 % must be increased 900 % to be toxic to 1% of the population

TI & margin of safety are only one measure to assess safety of drugs for use in medicine e.g digoxin has a TI of 2 and yet is very important in treating pt's with heart failure (one has to balance dangerous effects of disease vs side effects of drug)

The same applies to anticancerous drugs

3. Protective index (PI)

$$PI = \frac{\text{ED50 producing side effects}}{\text{ED50 producing desired effect}}$$

Considered the best measure to assess safety of drugs since most drugs produce side effects in doses lower than those which produce death

The larger the PI the better the drug

PI of 1 means that the dose which produces the desired effect in 50% of pt's still produces side effects in 50% of them

100

pt's 50

(%)

A   D   C

B

Log dose (mg)
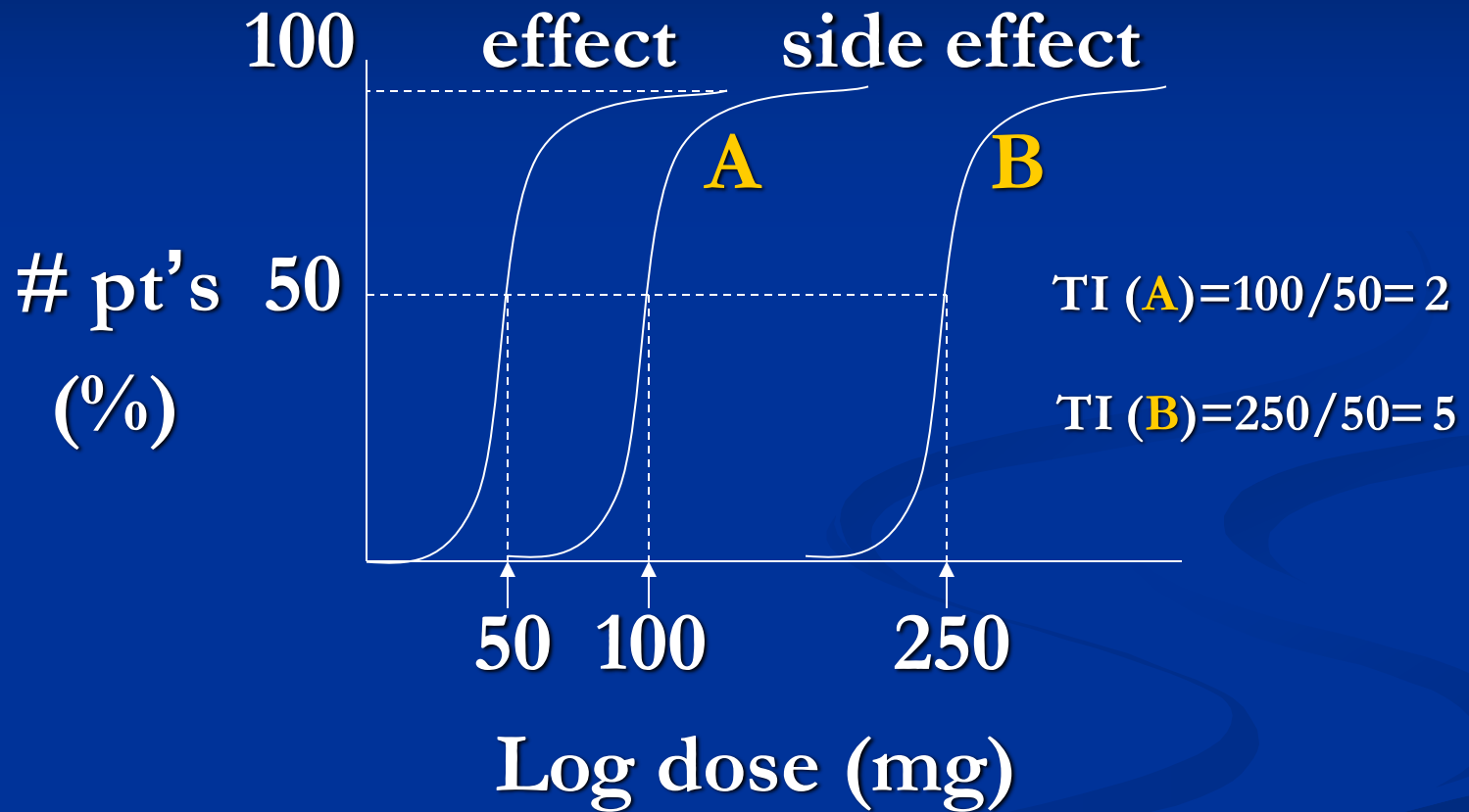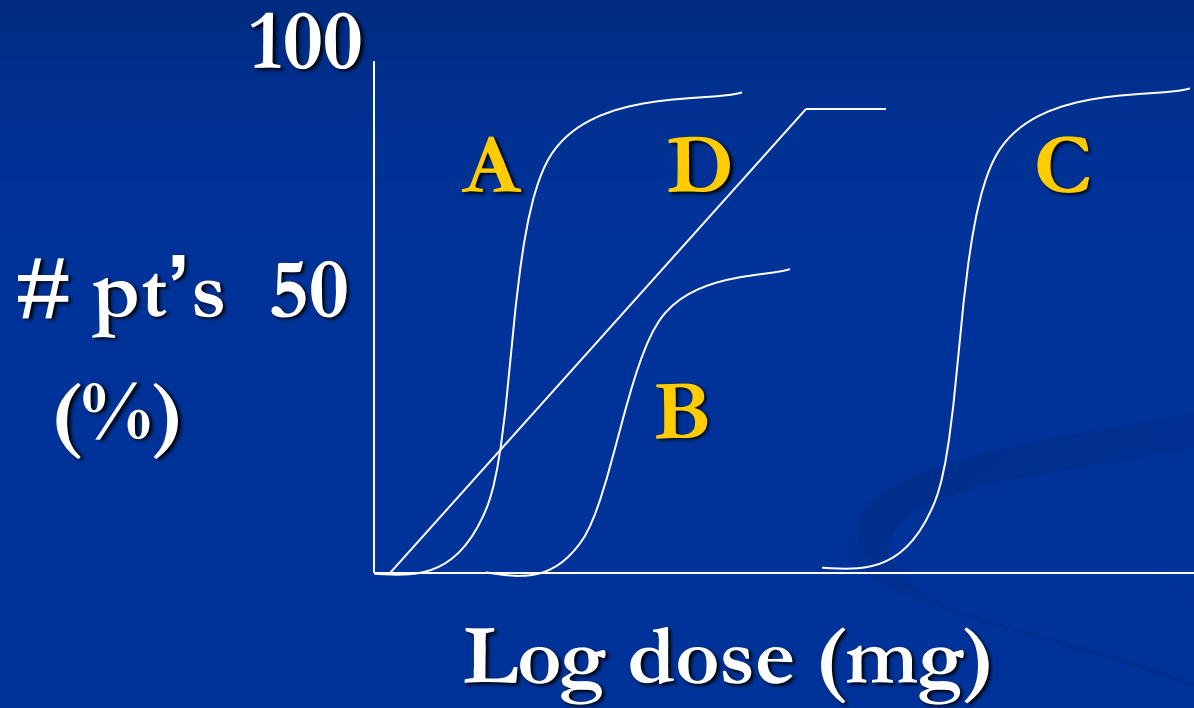
Types of drug-receptor interactions:

1. Drug agonism:

- Agonist (full agonist):

A drug that interacts with a specific receptor and produces maximum response

(strong agonist produces Vmax with low R occupancy; weak agonist has low efficacy but reaches Vmax with high R occupancy)

- Partial agonist

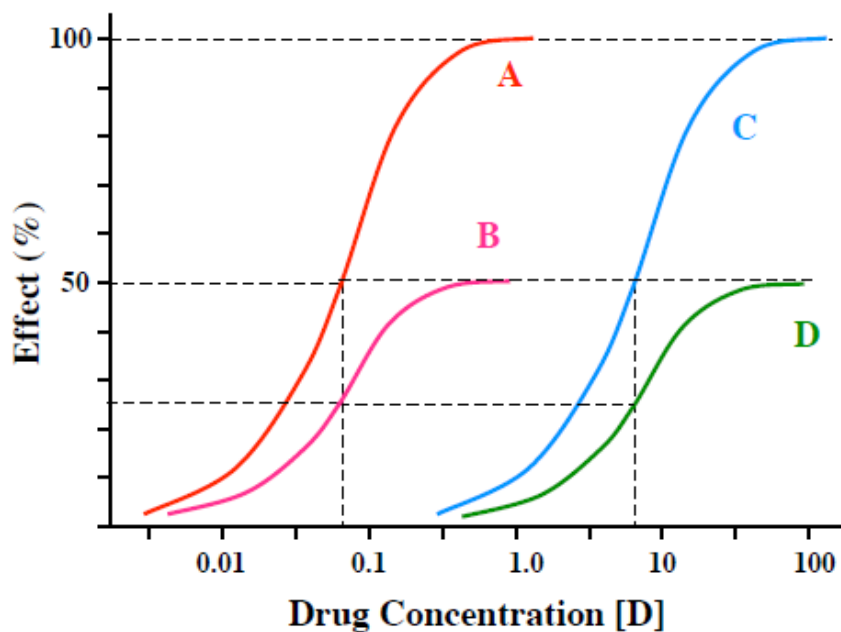A drug that has reduced efficacy but maximum potency and high affinity

- **Agonist-antagonistic agonists**

A drug which has both agonistic and antagonistic activities

- **Inverse agonist**

A drug that produces an effect opposite to agonist

A receptor which is capable of producing its biological response in the absence of a bound ligand is said to display "constitutive activity". The constitutive activity of receptors may be blocked by inverse agonist binding. Mutations in receptors that result in increased constitutive activity underlie some inherited diseases, such as precocious puberty (due to mutations in LH receptors) and hyperthyroidism (due to mutations in TSH receptors)

Inverse Agonists Reveal Constitutive Receptor Activity
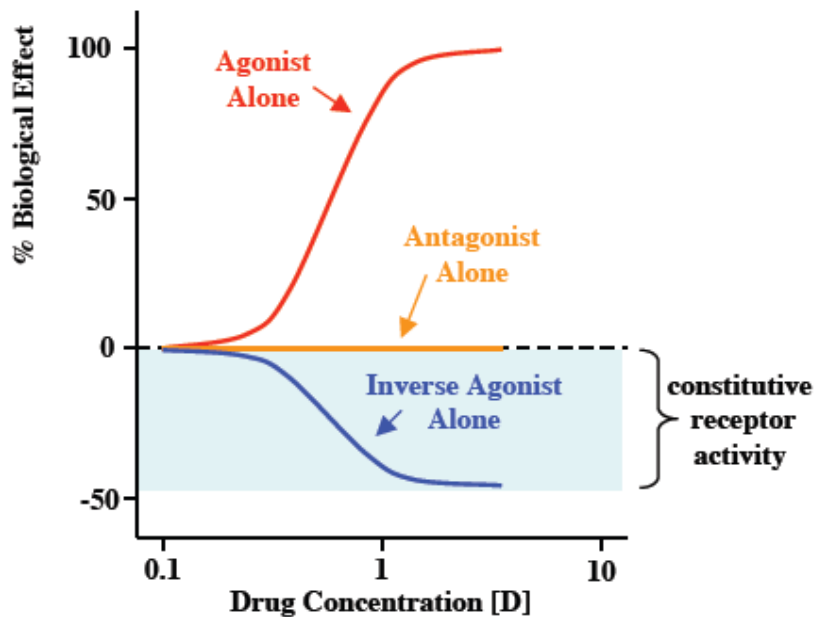
Agonist
- has an independent impact upon receptor activity

Antagonist
- impacts receptor activity only in the presence of agonist

Inverse Agonist
- has an independent impact upon receptor activity
- produces an effect opposite to agonist

Addition: Applies whenever two drugs producing similar response given together result in a final response equals to the sum of the response of each drug (1+1=2)

Synergism: Applies whenever two drugs producing similar response given together result in a final response greater than the sum of the response of individual drugs (1+1=3 or 5…)

Potentiation: Applies when one drug producing no response given with another producing a specific response results in an increase in the final response of the second drug (0+1=2 or 5…)

Spare Receptors

- In some systems, full agonists are capable of eliciting 50% response with less than 50% of the receptors bound (receptor occupancy)
- Pool of available receptors exceeds the number required for a full response
- Common for receptors that bind hormones and neurotransmitters

Receptor Occupancy *versus* Physiological Response
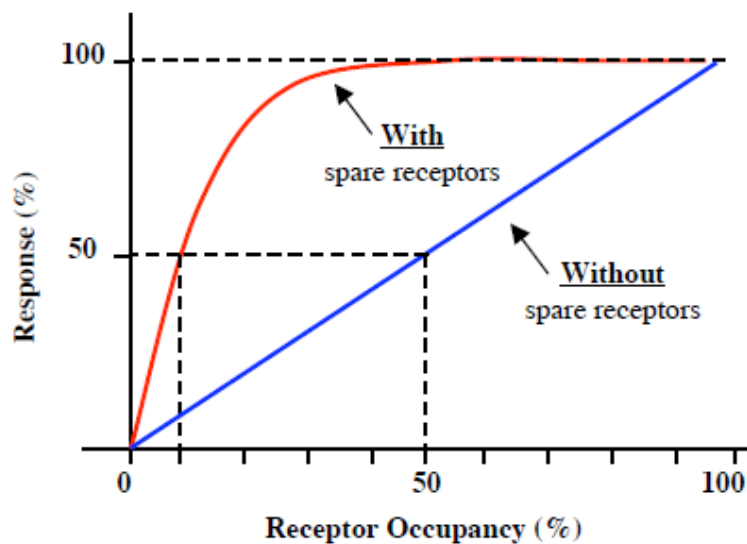
Without spare receptors:

- *50% response = 50% occupancy*
- *Biological effect is proportional to [DR] at all drug concentrations*

With spare receptors:

- *50% response = 10% occupancy*
- *Biological effect is proportional to [DR] only at low drug concentrations*
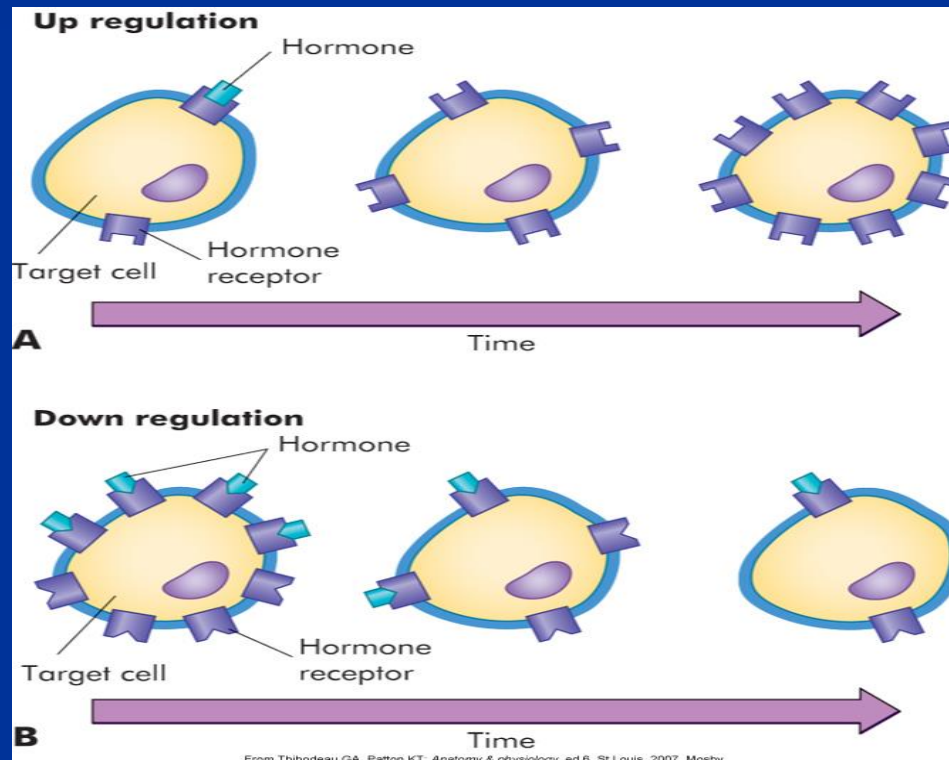
Spare receptors:

Some agonists may lead to 50% of response with less than 50% of the receptors bound (receptor occupancy)

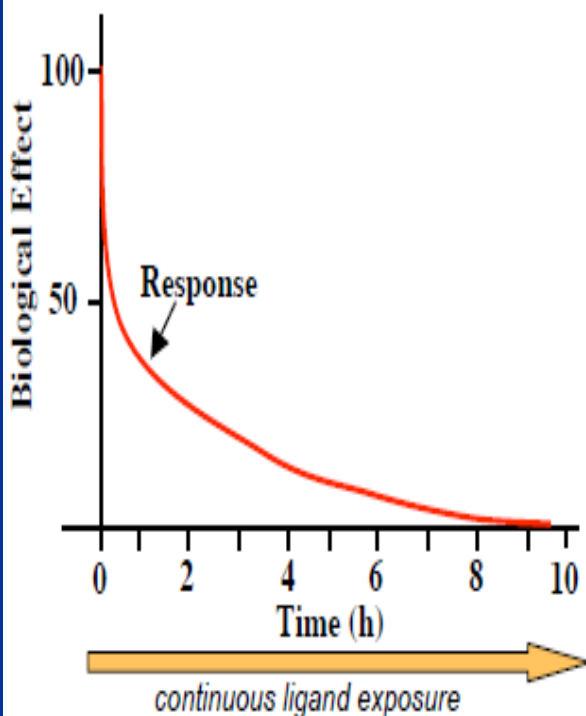The pool of available receptors exceeds the no. required for a full response

e.g. hormones (insulin); neurotransmitters (E; NE)

Receptors are subject to either upregulation or downregulation

Up regulation
Hormone
Hormone receptor
Target cell
A
Time

Down regulation
Hormone
Hormone receptor
Target cell
B
Time

From Thibodeau GA, Patton KT: *Anatomy & physiology*, ed 6, St Louis, 2007, Mosby.

2. Drug antagonism:

A pure antagonist is a drug which binds a specific receptor producing no effect or response , but if given with an agonist it reverses the effect of the agonist

Antagonism may take many forms:

a. Physiologic antagonism:

Sympathetic vs parasympathetic

b. Antagonism by neutralization:

Applies whenever two drugs given together form an inactive complex

c. Pharmacologic antagonism: 2 major types

1. Surmountable antagonism (competitive; equilibrium; reversible)
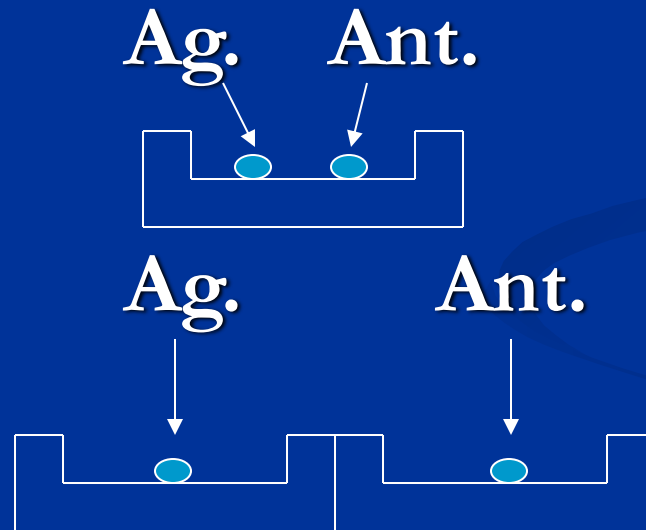
Ag. Ant. Ag. Ant.

Characteristics of competitive antagonism:

- Both Agonist and antagonist compete directly for the same receptor or even site

- It is reversible

- ED50 of agonist ↑ in presence of antagonist (affinity ↓ and potency=relative affinity ↓)

- No change in total # of receptors

- No change in Vmax

- Dose-response curves are shifted to the right
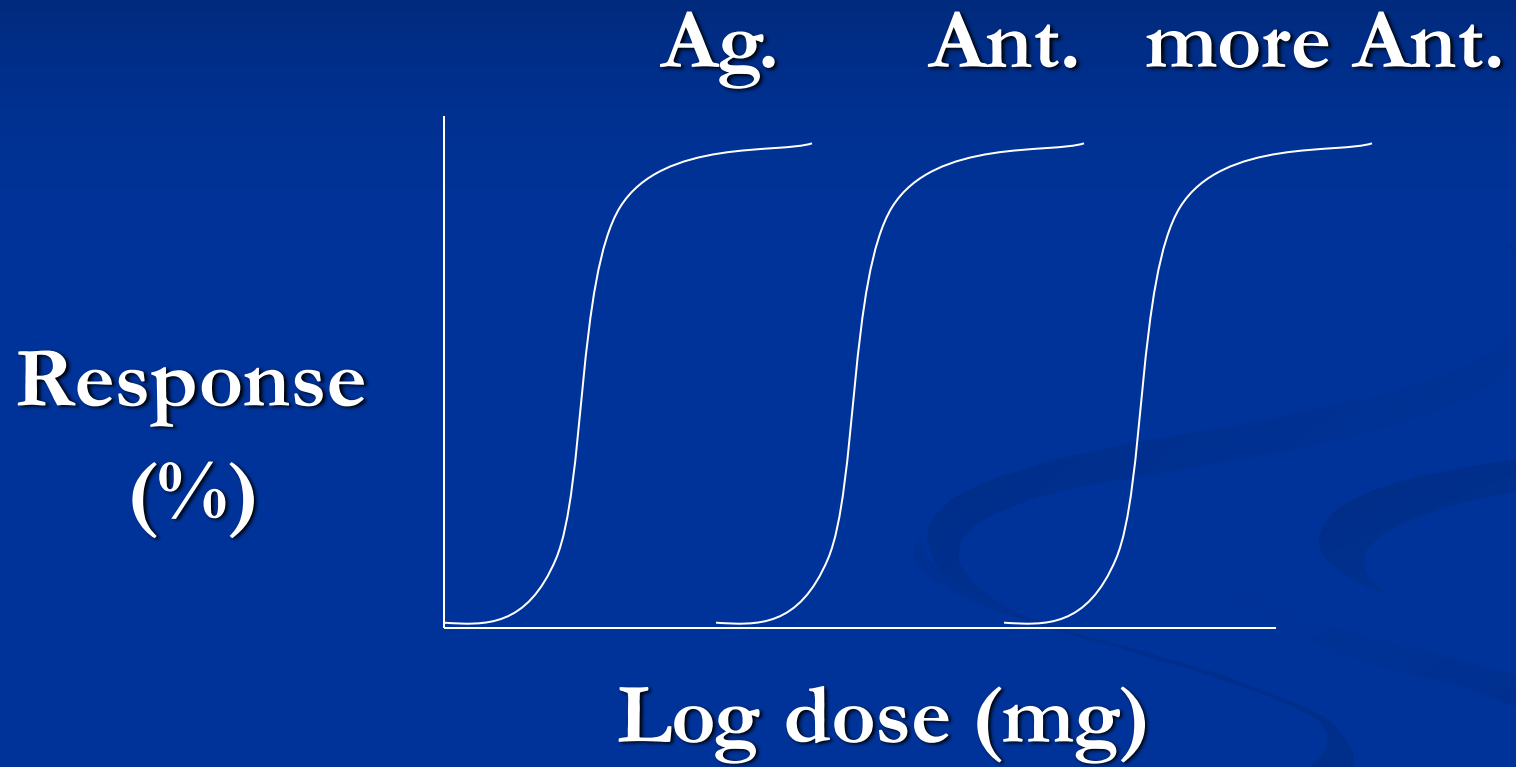
2. Unsurmountable antagonism: 2 types

- Noncompetitive=uncompetitive=irrevers.

- Competitive nonequilibrium irreversible

Both the agonist and the antagonist bind at the same receptor site. However the antagonist binds irreversibly (forms a covalent bond) with the receptor and can't displace the agonist

Ag. An<u>t</u>. Ag. Ant.
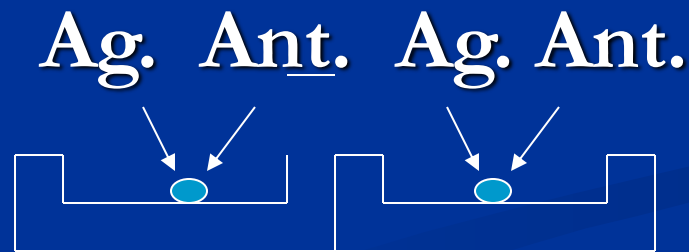
Characteristics of noncompetitive antagonism:

- Both Agonist and antagonist act on different sites of a given receptor or even different receptors

- It is irreversible; ↑ dose of agonist produces no pharmacological response

- Vmax ↓ with increasing dose of antagonist

- Results in no change in the ED_{50} of agonist (no change in affinity or potency) but results in ↓ in Vmax

- Total # of receptors ↓

- Results in downward shift in the Dose-response curves