Al- Anbar university - College of Medicine - Pharmacology department

Lec. 5,6

pharmacodynamics

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- In Greek

Pharmacon = Drug

Dynamics = Action/Power

It covers all the aspects relating to
"What a drug does to the body"

Mechanism of action

- Action: How and Where the effect is produced is called as Action.

- Effect: The type of response producing by drug.

Site of Drug Action

- Where:

1. Extra cellular
2. Cellular
3. Intracellular

Types of Drug Action

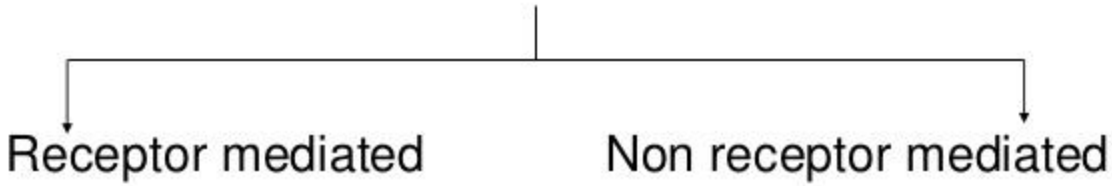
EFFECT (Type of responses):-

1. Stimulation
2. Inhibition/Depression
3. Replacement
4. Irritation
5. Cytotoxic

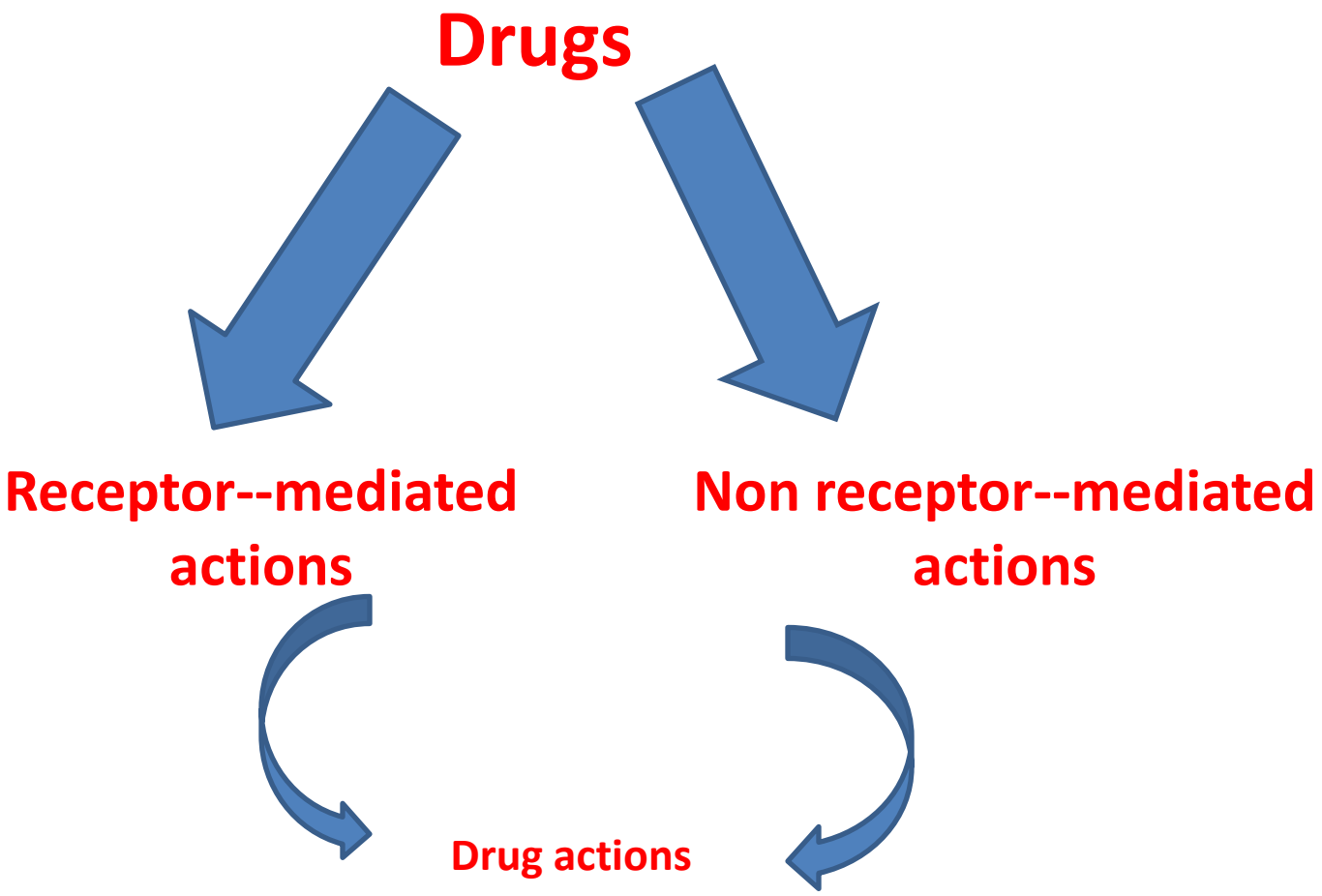
Mechanism of Action of Drugs

- Drug act either by receptor or by non receptor or by targeting specific genetic changes.

Majority of drugs acts by (HOW)



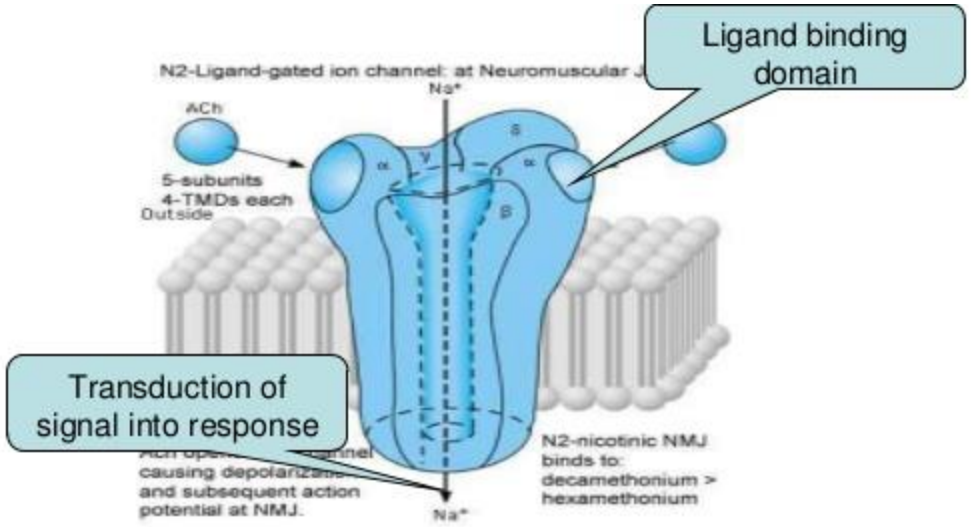
What are the mechanisms of drug action?



Receptor Mediated action

- Drug produce their effect through interacting with some chemical compartment of living organism c/s Receptor.

- Receptors are macromolecules
- Most are proteins
- Present either on the cell surface, cytoplasm or in the nucleus



Receptor Functions : Two essential functions

- 1. Recognization of specific ligand molecule (Ligand binding domain)
- 2. Transduction of signal into response (Effector domain)

Drugs may act by different mechanisms: -

Receptor interaction Many drugs act by activating or blocking a receptor.

Non receptor –mediated mechanisms

1-. ENZYME INHIBITION e.g. monoamine oxidase (deprenyl), cholinesterase (neostigmine), cyclooxygenase (aspirin).

2-. CHEMICAL INTERACTION e.g. gastric acid (antacids), urine alkalinizing agent (potassium sodium hydrogen citrate), heparin (protamine sulphate), alkylating agents.

3-. PHYSICO-CHEMICAL PROPERTIES e.g. osmotic diuretics, laxatives, volatile anesthetics.

4- Ion channels.

– Na-channel blockers (local anesthetics).

– Ca-channel blockers (channel blockers (antiarrhythmic).

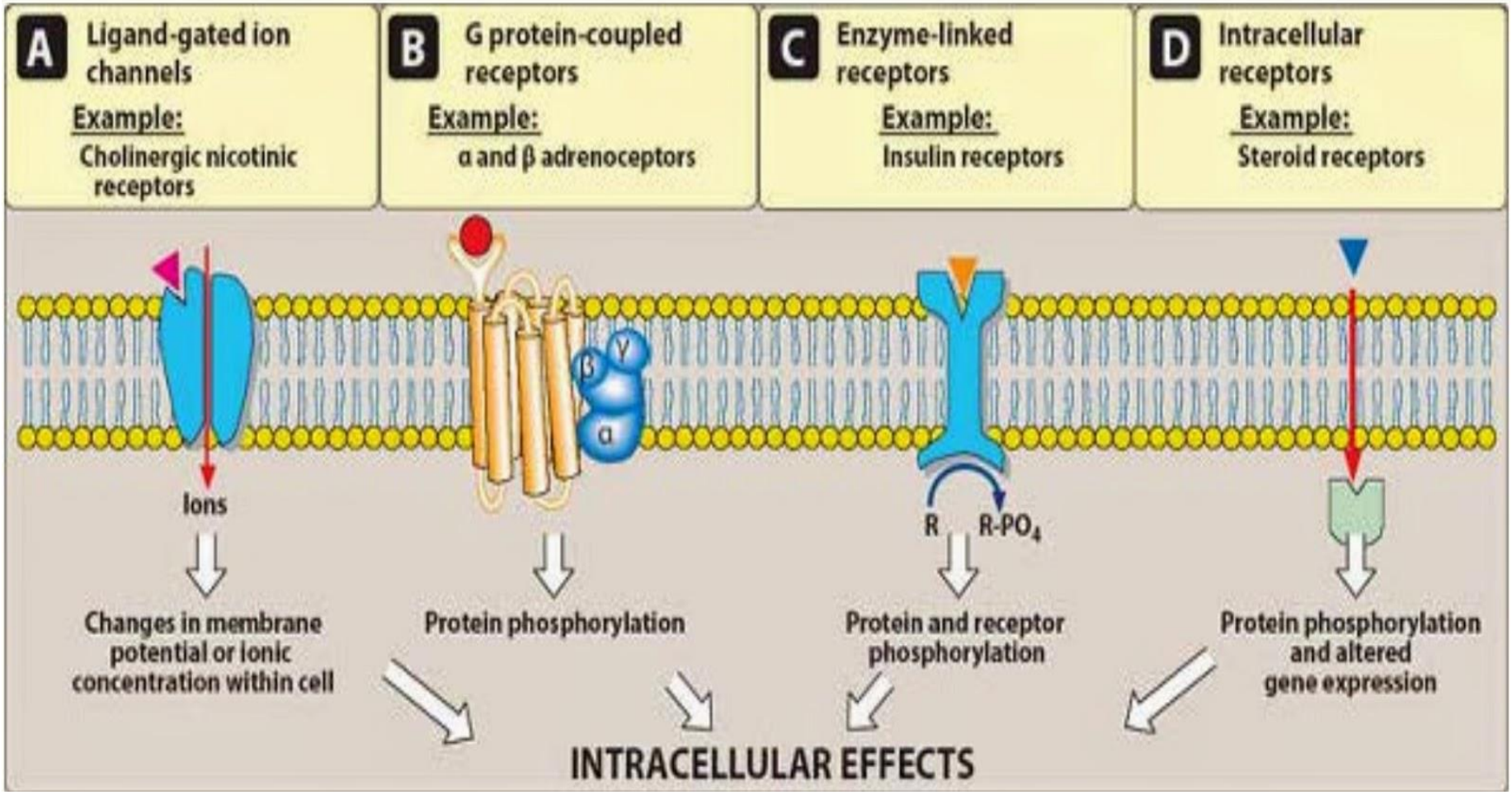
Druge: - “Any substance that brings a **change in biologic function** through its chemical actions”

Receptors: - A specific macromolecule protein in either the plasma membrane or interior of a target cell with which a chemical messenger/drug combines

Receptor families

Four types of receptors families

1. Ligand-gated ion channels (inotropic receptors)
2. G-protien coupled receptor (Metabotropic receptors)
3. Enzymatic receptors (tyrosinekinase)
4. Receptor regulating gene expression (transcription factors/ Steroid)


A
Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B
G protein-coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
Ions
β
γ
α
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

- **Drug binds to receptor and activates the receptor so produce a response (agonist)**

or binds to receptor but produces no action (antagonist).

Affinity :- Ability of a drug to combine with the receptor So, a pharmacological response depends on the affinity and efficacy.

selectivity :- degree of complimentary co relation between drug and receptor.

Ligand: any molecule which attaches selectively to particular receptors or sites (only binding or affinity).

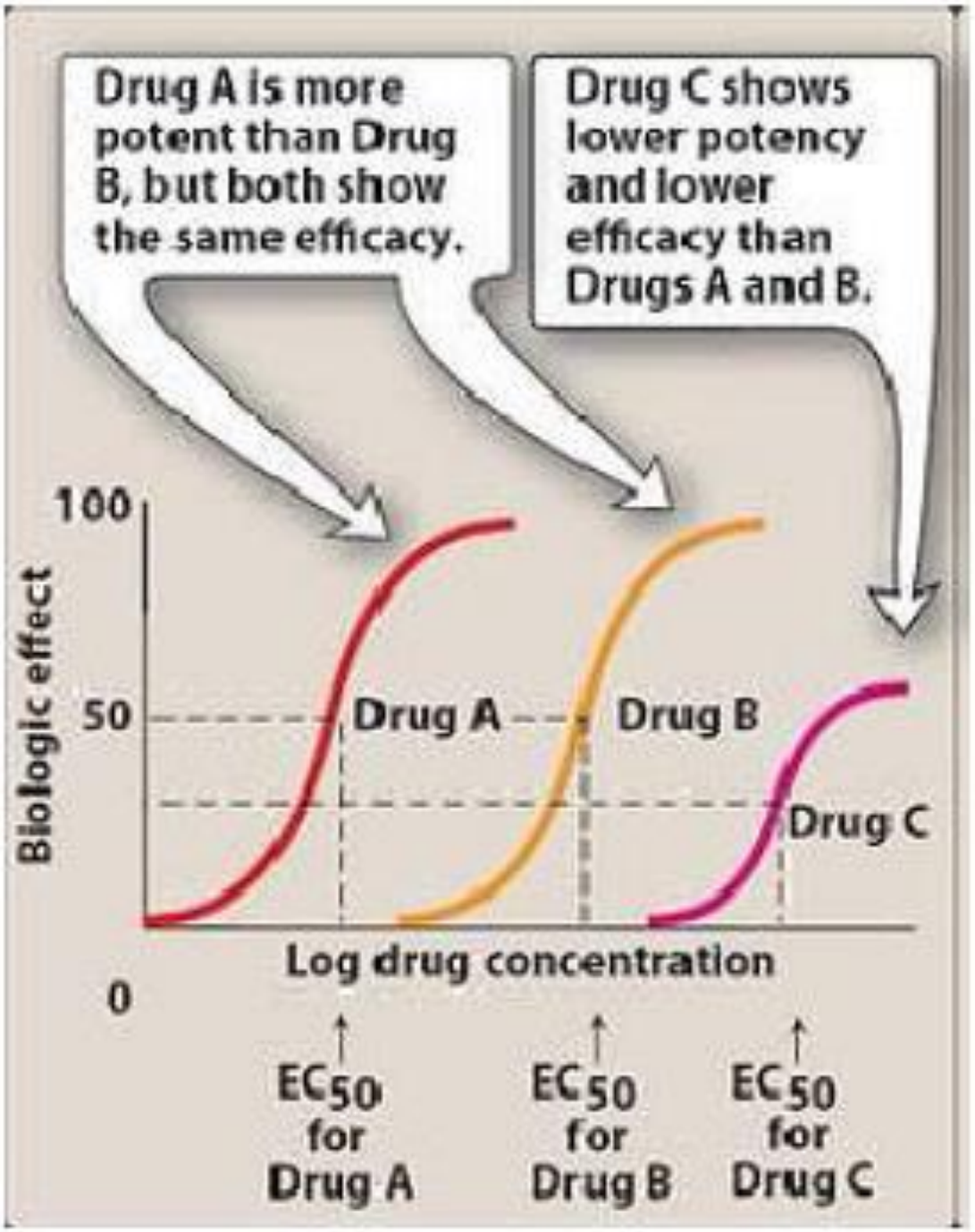
Efficacy (Intrinsic Activity) (IA)

– **Capacity of a drug to activate receptor and produce action.**
– **is the ability of the drug to produce maximum response (E max).**
- After making drug receptor complex.

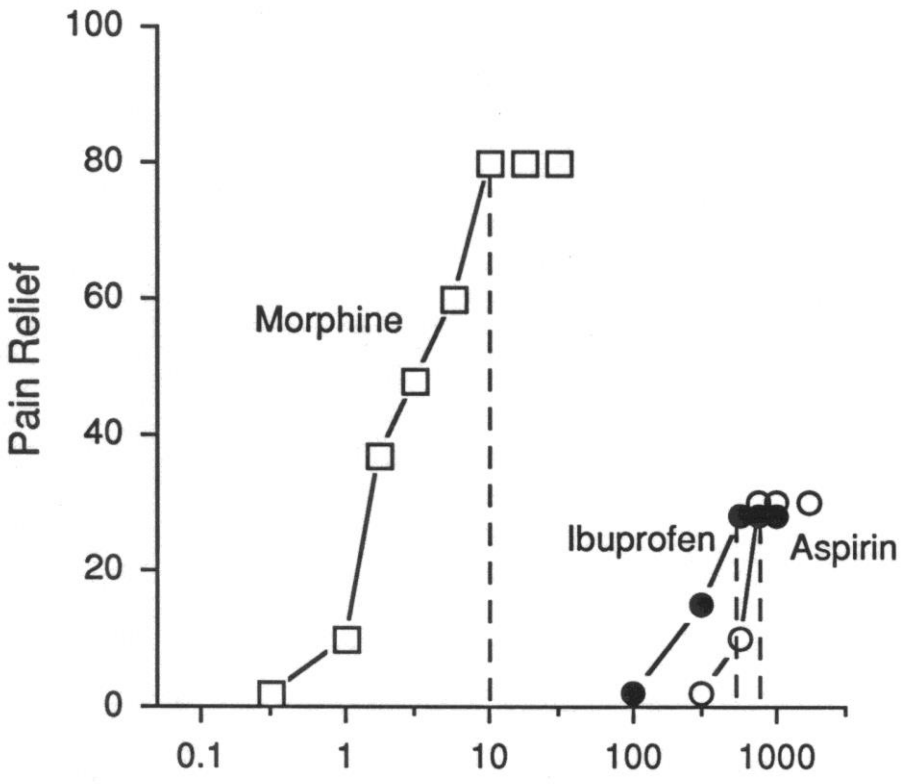
Potancy: - (EC50 or ED50): the concentration or dose needed to produce a 50% maximal response.

Agonist : - is a drug that combines with receptor and produce a response (has affinity and efficacy).

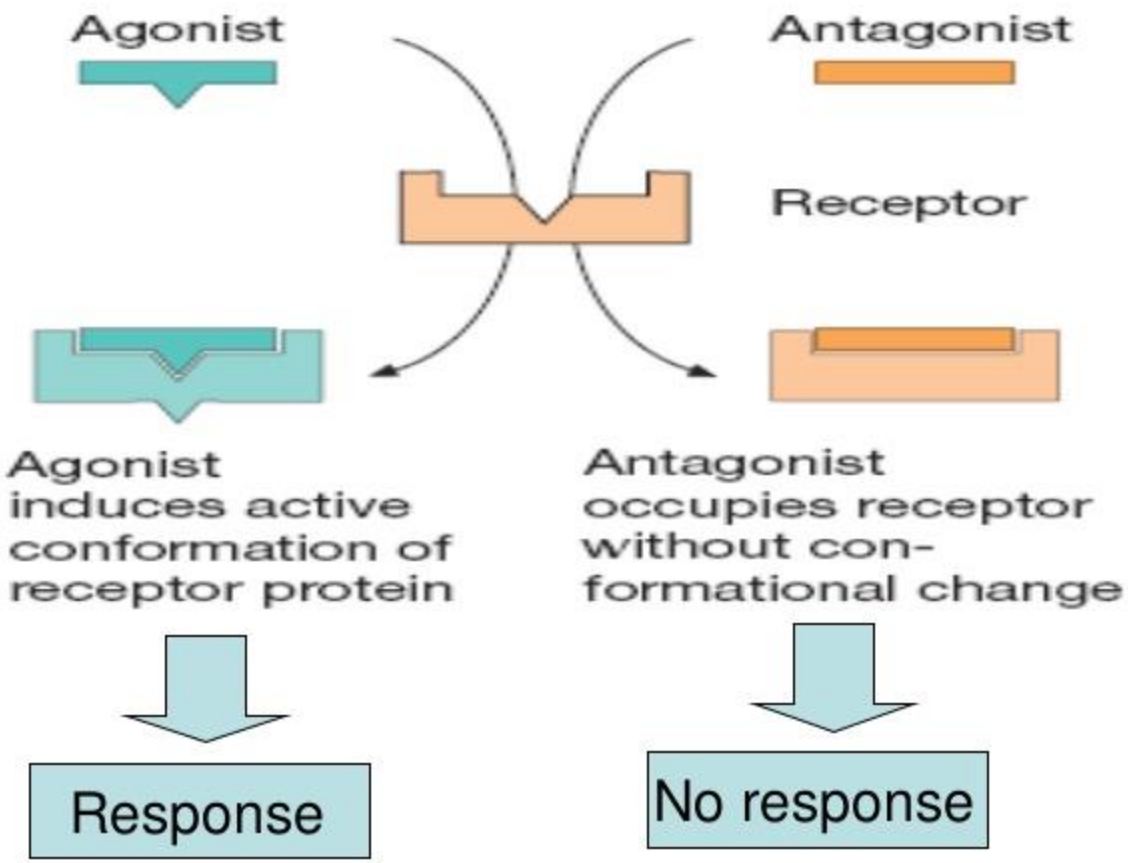
Antagonist : - is a drug that combines with a receptor without producing responses. It blocks the action of the agonist (Has affinity but no or zero efficacy). It has structural similarity to agonist.


Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

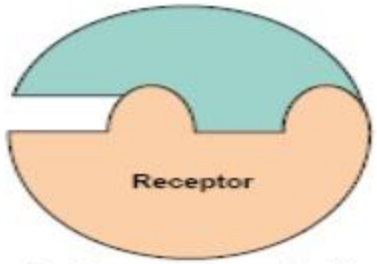
Efficacy



- Maximum possible effect relative to other agents
- Indicated by peak of D-R curve
- Full agonist = 100% efficacy
- Partial agonist = 50% efficacy
- Antagonist = 0% efficacy
- Inverse agonist = -100% efficacy


Agonist
Antagonist
Receptor
Agonist induces active conformation of receptor protein
Antagonist occupies receptor without con-formational change
Response
No response

- Partial agonist :These drug have full affinity to receptor but with low intrinsic activity (IA=0 to 1).
- These are only partly as effective as agonist



C. Some drug-receptor fit. Slight therapeutic response possible.

(Affinity is lesser when comparison to agonist)

Ex: Pindolol, Pentazocine

- Inverse agonist: These have full affinity towards the receptor but intrinsic activity is zero to -1 i.e., produces effect is just opposite to that of agonist.

Ex:- ß-Carboline is inverse agonist for Benzodiazepines receptors.

Thank you

Types of agonists

- ❑ **Full agonist.**
- ❑ **Partial agonist.**
- ❑ **Inverse agonist.**

Full Agonist

- **A drug that combines with its specific receptor to produce maximal effect .**
- **It Has both high affinity & full efficacy.**

Partial Agonist

- ❖ A drug that combines with its specific receptor to produce submaximal effect regardless of concentration (Full receptor occupancy).
- ❖ It has high affinity & partial efficacy.

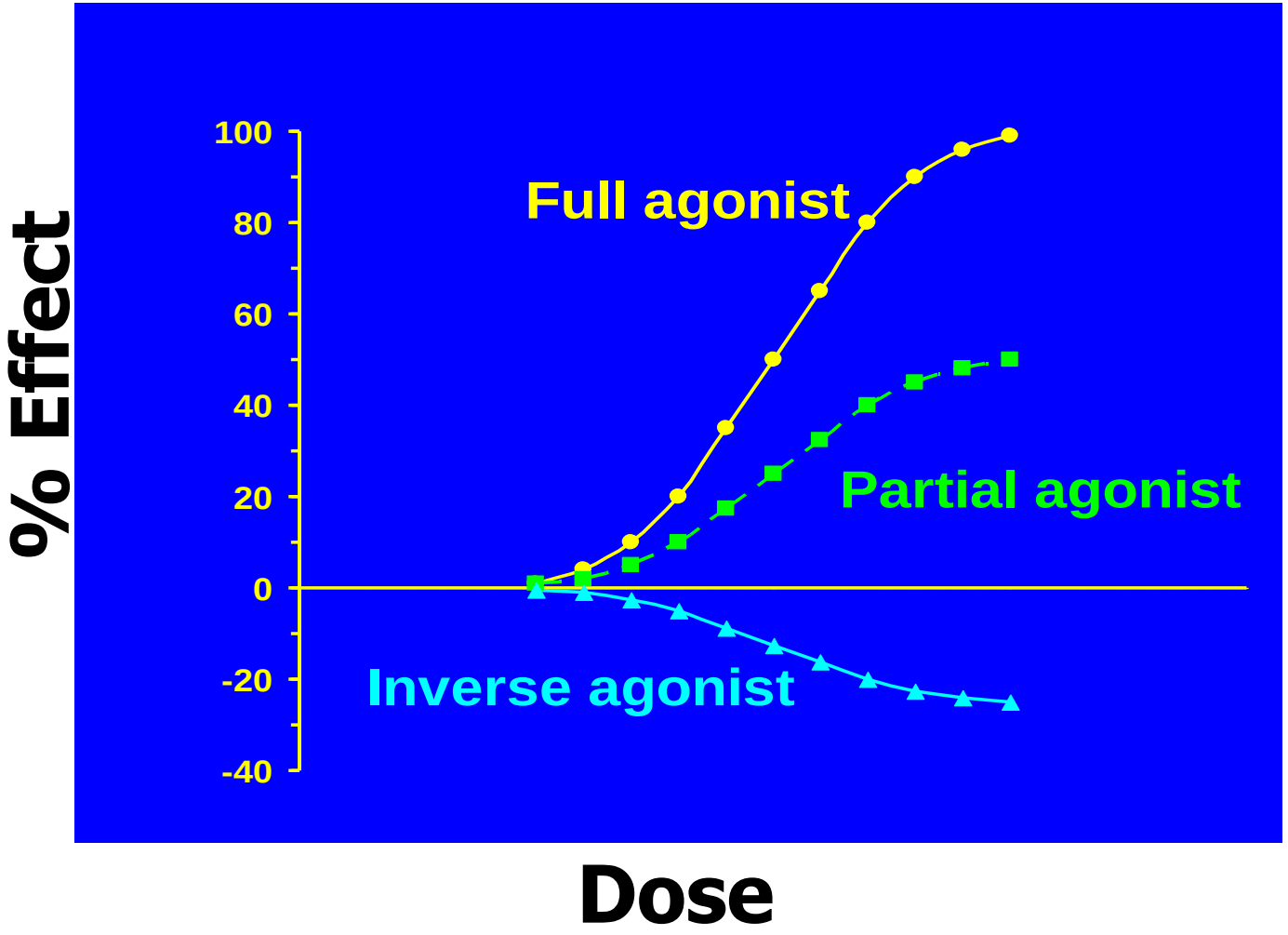
Inverse Agonist .

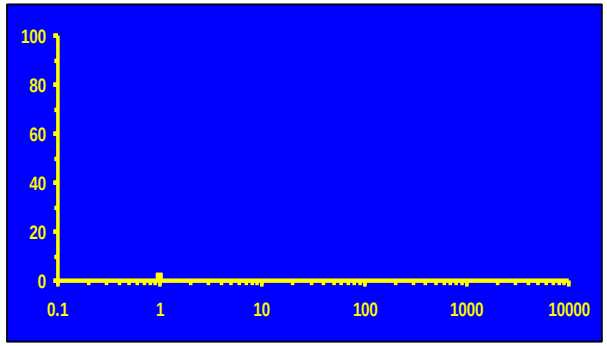
- ❑ combines with its receptor & produce response opposite to those of the agonist.
- ❑ It has high affinity & negative efficacy.

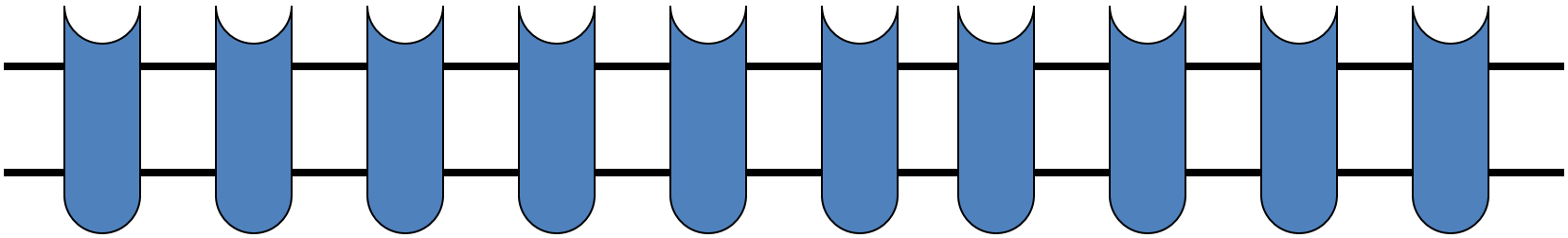
If explained in terms of affinity and IA (efficacy):

- Agonist: Affinity + IA (1)
- Antagonist: Affinity + IA (0)
- Partial agonist: Affinity + IA (0-1)
- Inverse agonist: Affinity + IA (0 to -1)

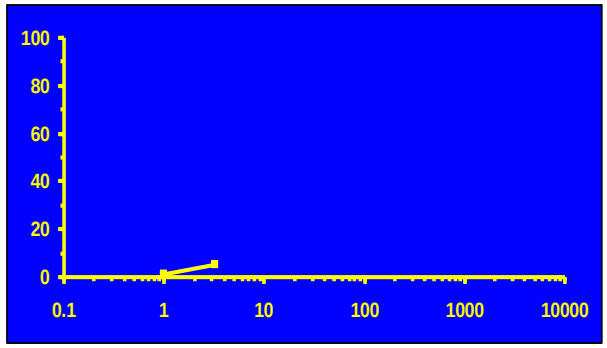
Inverse Agonist

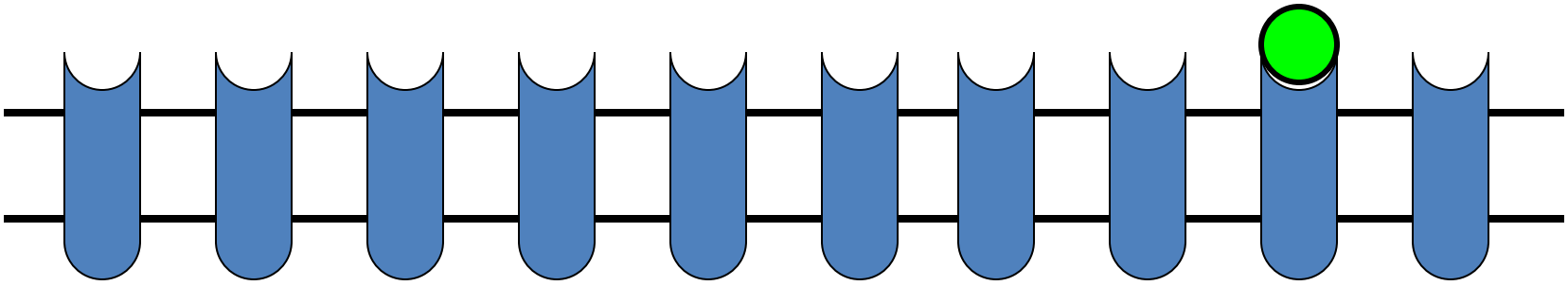




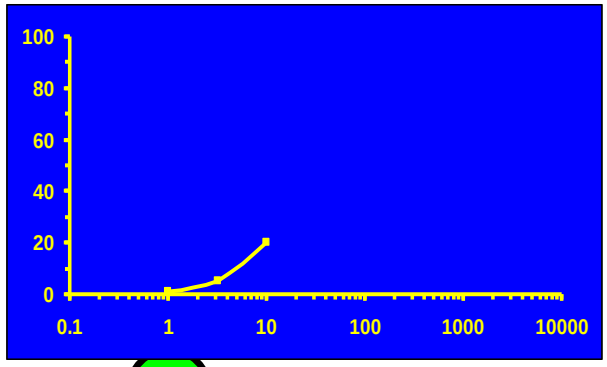


= Agonist





= Agonist



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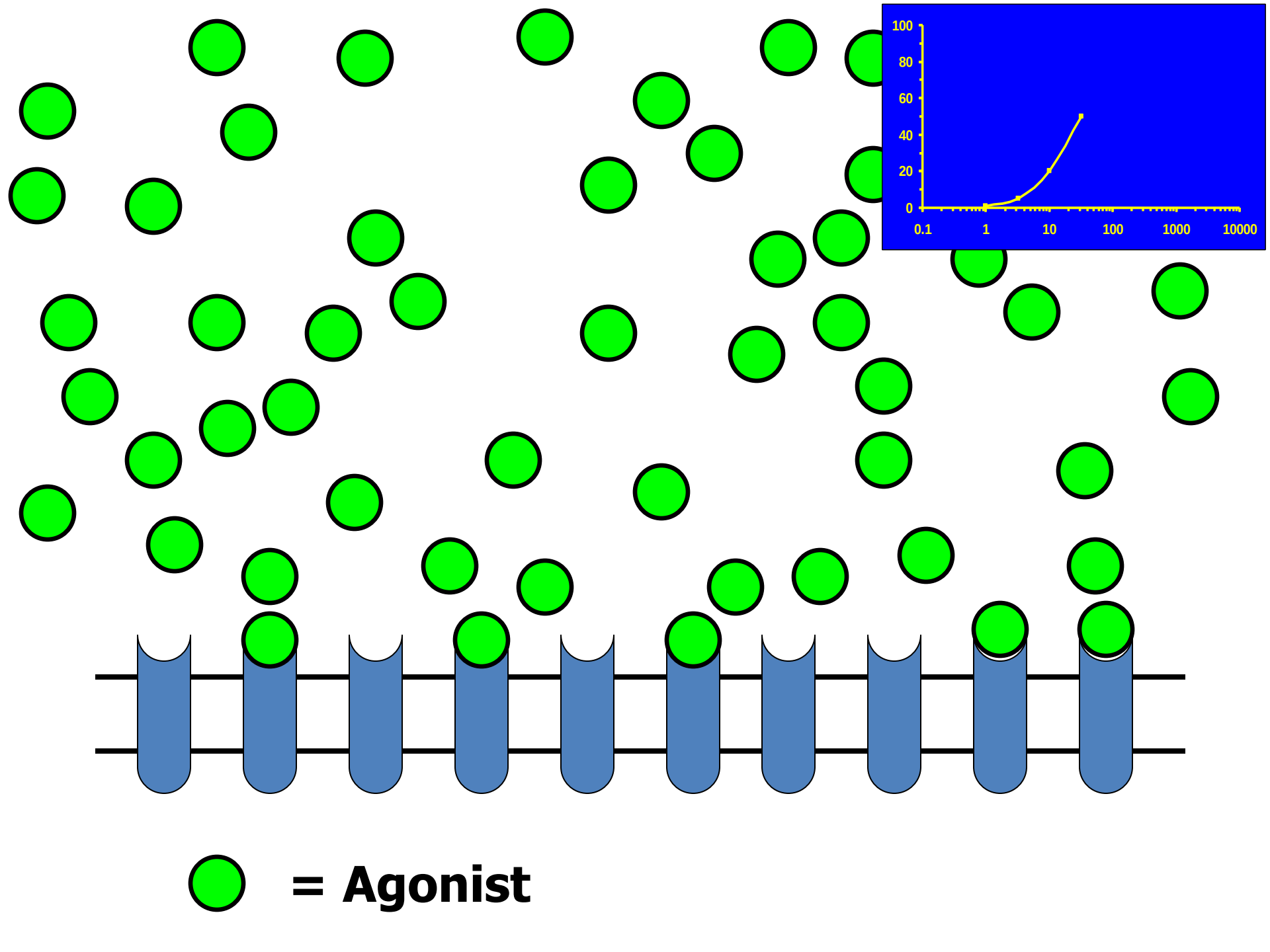
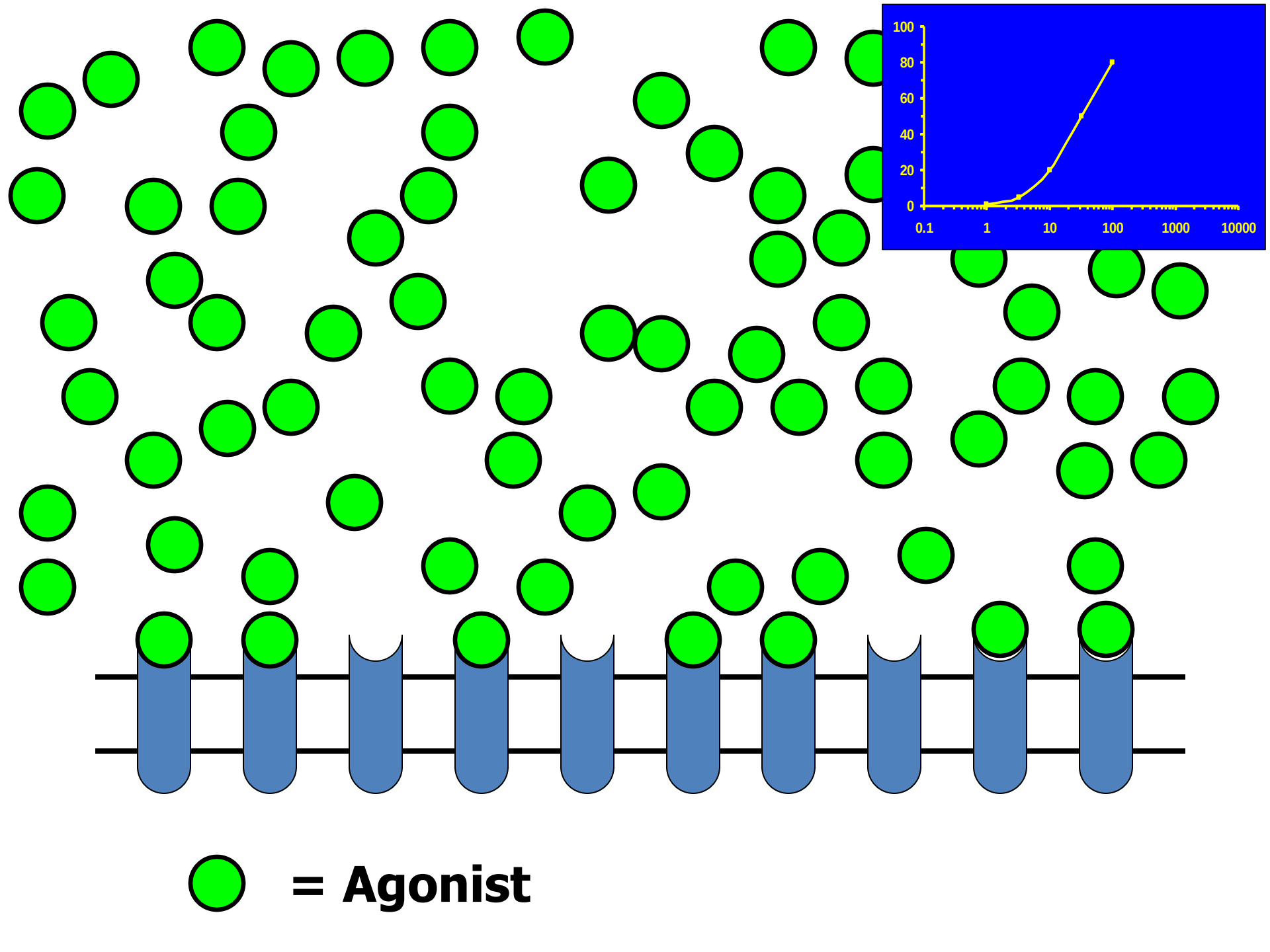

100
80
60
40
20
0
0.1
1
10
100
1000
10000
= Agonist


100
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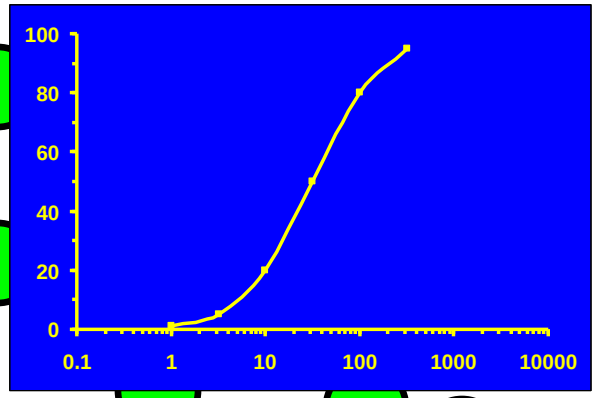

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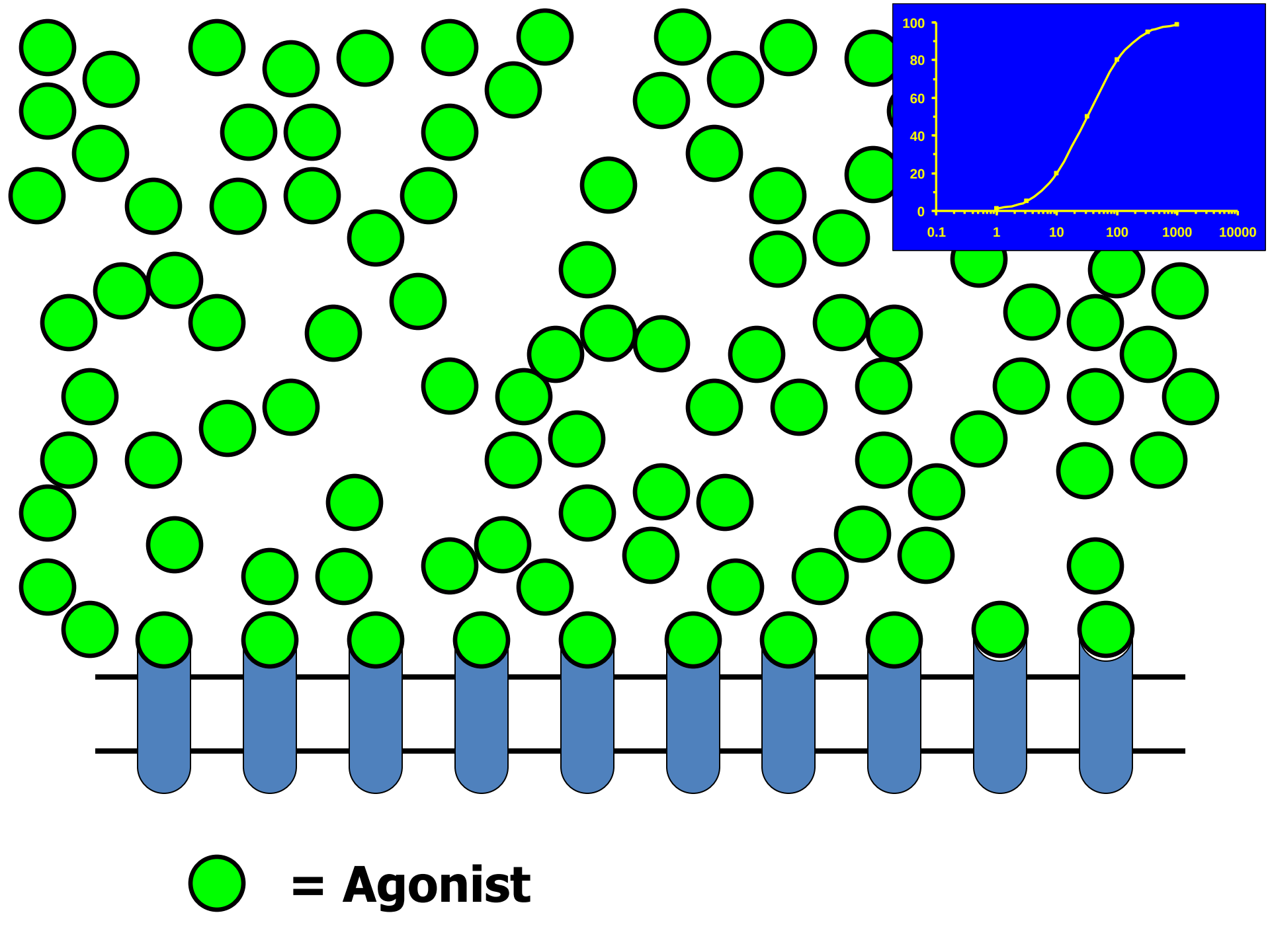
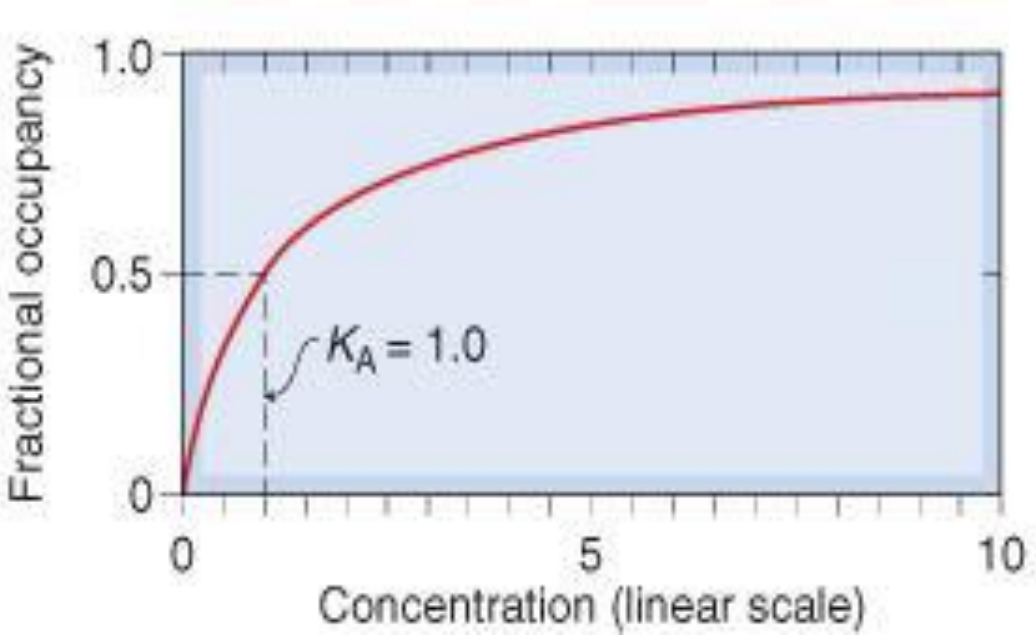

100
80
60
40
20
0
0.1
1
10
100
1000
10000
= Agonist

- Drug + Receptor → Drug-Receptor Complex → response

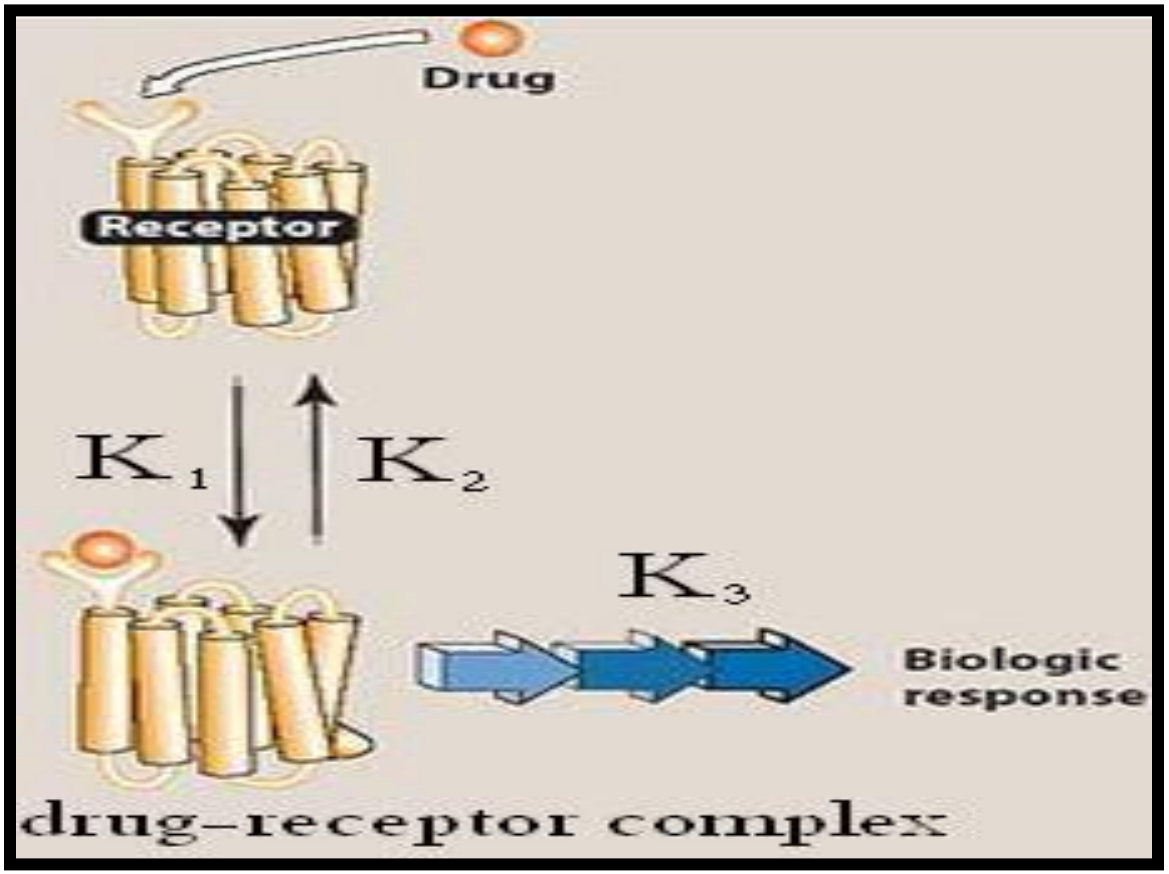
Dose Response Curves

A pharmacological response is a function of the dose or concentration of a drug. **Dose response curves are graphical representation of the relationship between dose and response**. Usually, it is convenient to have log scale on axis of drug concentration.



- Most drugs produce their actions by interacting with receptors.

- **Drug +receptor → drug-receptor complex → response**



- *(in the diagram)* → K1 = association constant
  K2 = dissociation constant
  K3 = efficacy
- K1 and K2 depend on *affinity* and *occupancy*

Occupancy: fraction of receptors occupied to the total number of receptors.

Drug-receptor binding

- **Drug +receptor → drug-receptor complex → response.**
- 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

Types of dose response curves

.Graded dose response curves

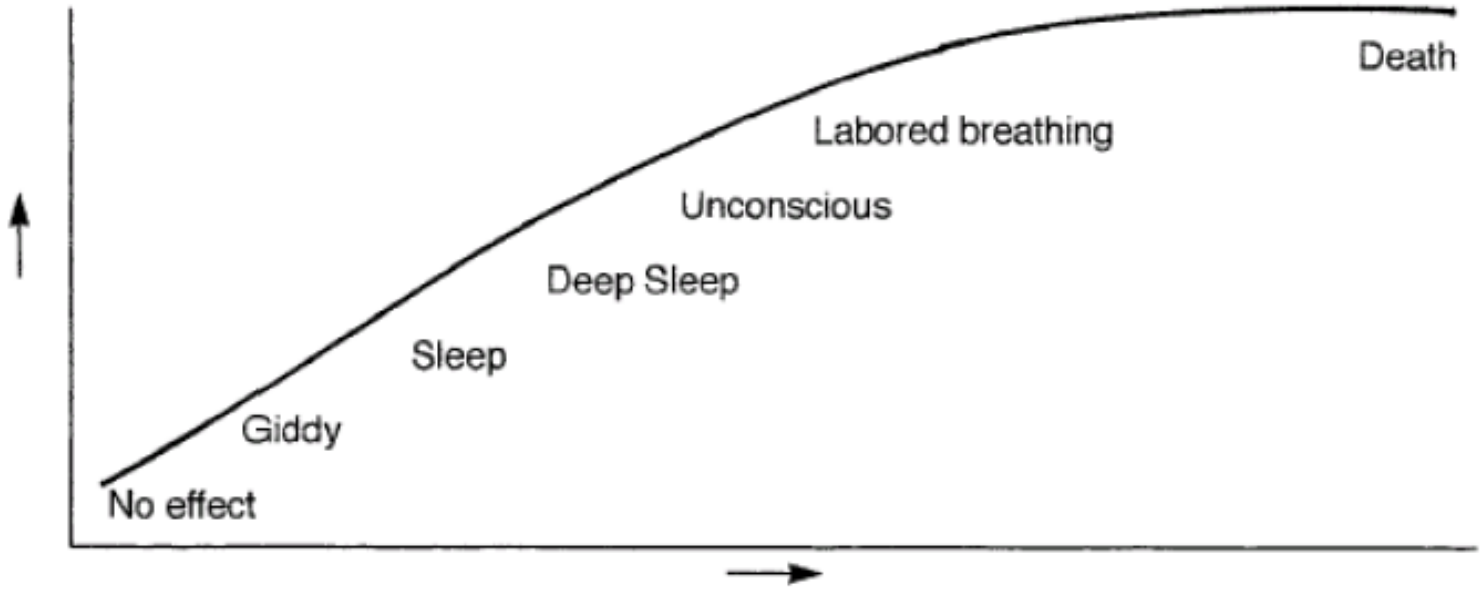
.Quantal dose response curves

- A graph of the relationship between dose and response.
- *minimum detectable response* and a *maximum response* by varying the dose or drug concentration,

- Graded dose response curve indicates (maximum efficacy)
- Quantal dose response indicates potential variability of responsiveness among individuals

Exposure to ethanol
Graded responses between no effect and death

Dose-Response Curves

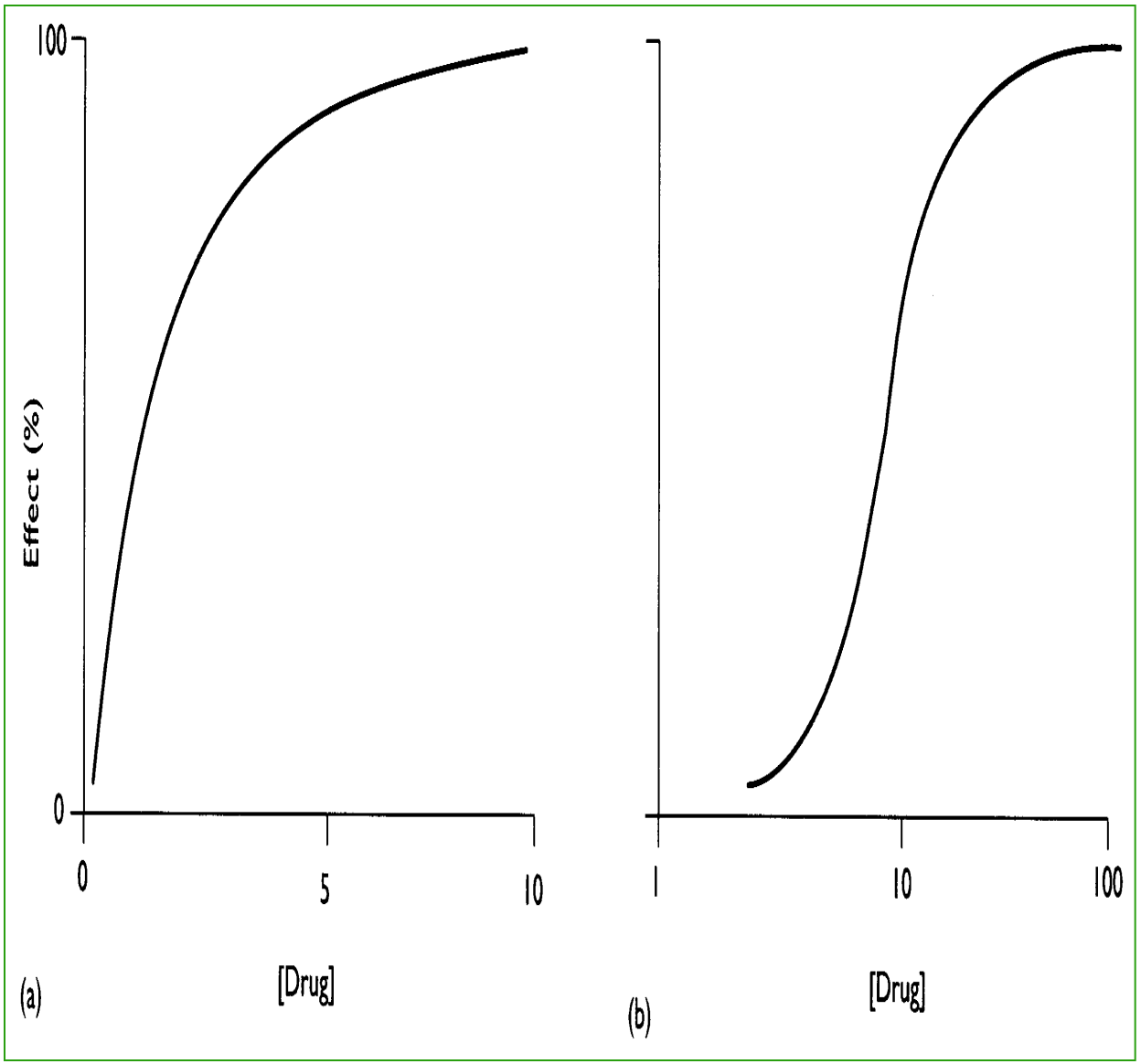


Quantal Dose-Response Curves

- 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.**

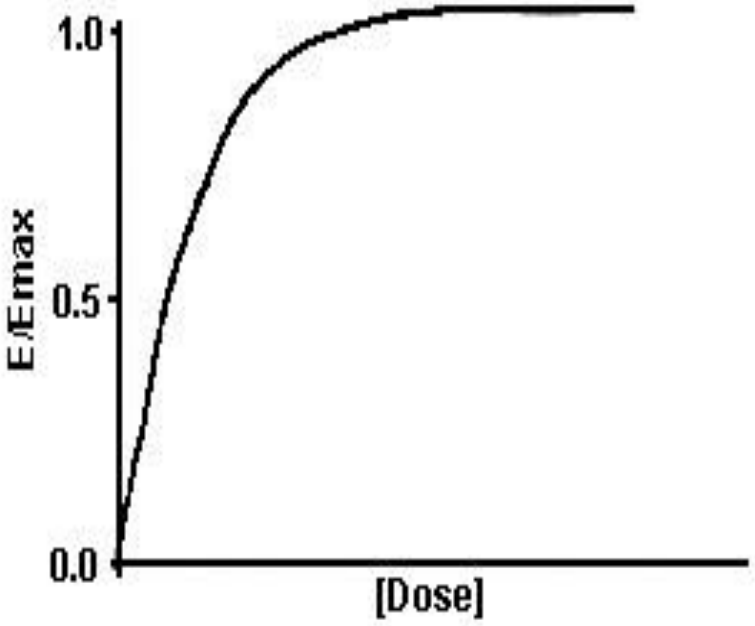
The numbers of receptors may be altered during chronic drug treatment, with either an increase in receptor numbers (**up-regulation** – e.g. beta-antagonists) or a decrease (**down-regulation** – desensitization: e.g. beta-2 agonists).

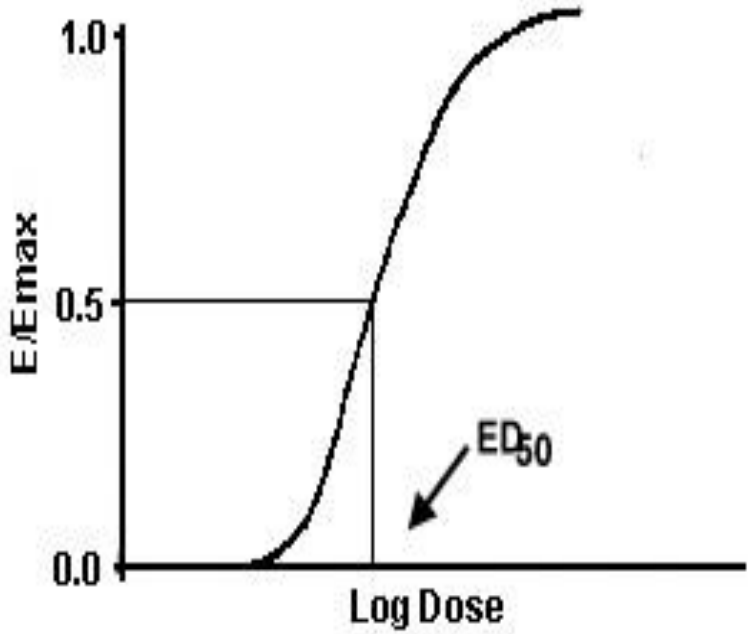
Plotted dose-response curves:



Hyperbolic shape (a)

Sigmoidal shape (b)


1.0
0.5
0.0
E/Emax
[Dose]


1.0
0.5
0.0
E/Emax
ED50
Log Dose

- We usually use the log of a drug's concentration (instead of using the concentration value itself). This will help use to plot the curve even in extremely low concentrations of drugs.

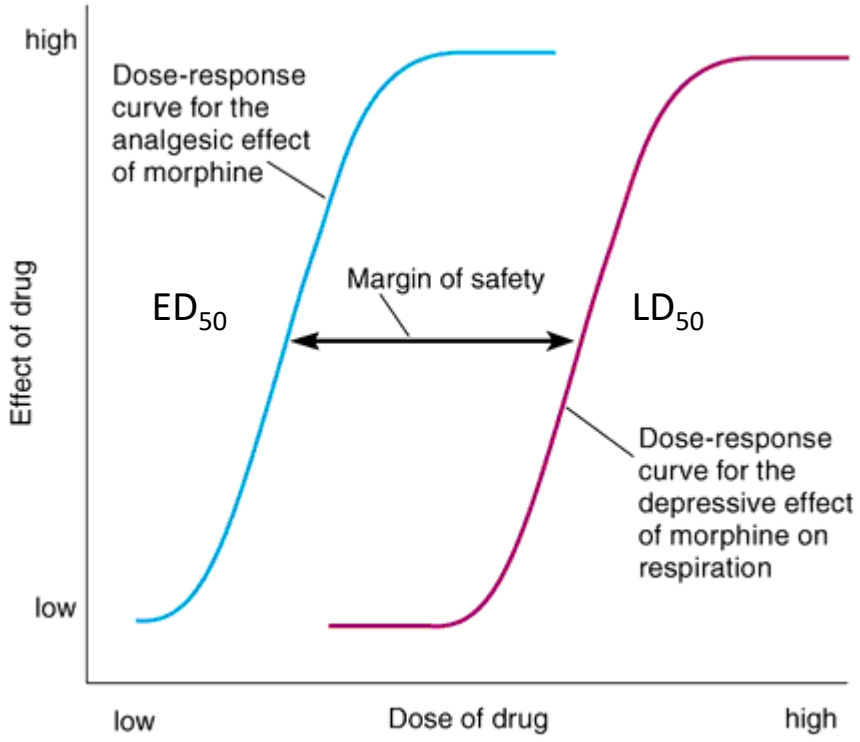
- It makes a *sigmoid* (s-shaped) curve *(instead of hyperbolic)*

- 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

Therapeutic Index

- Effective dose (ED_{50}) = dose at which 50% population shows response
- Lethal dose (LD_{50}) =dose at which 50% population dies
- TI = LD_{50}/ED_{50}, an indication of safety of a drug (higher is better)



Therapeutic Index: (safety of drugs)

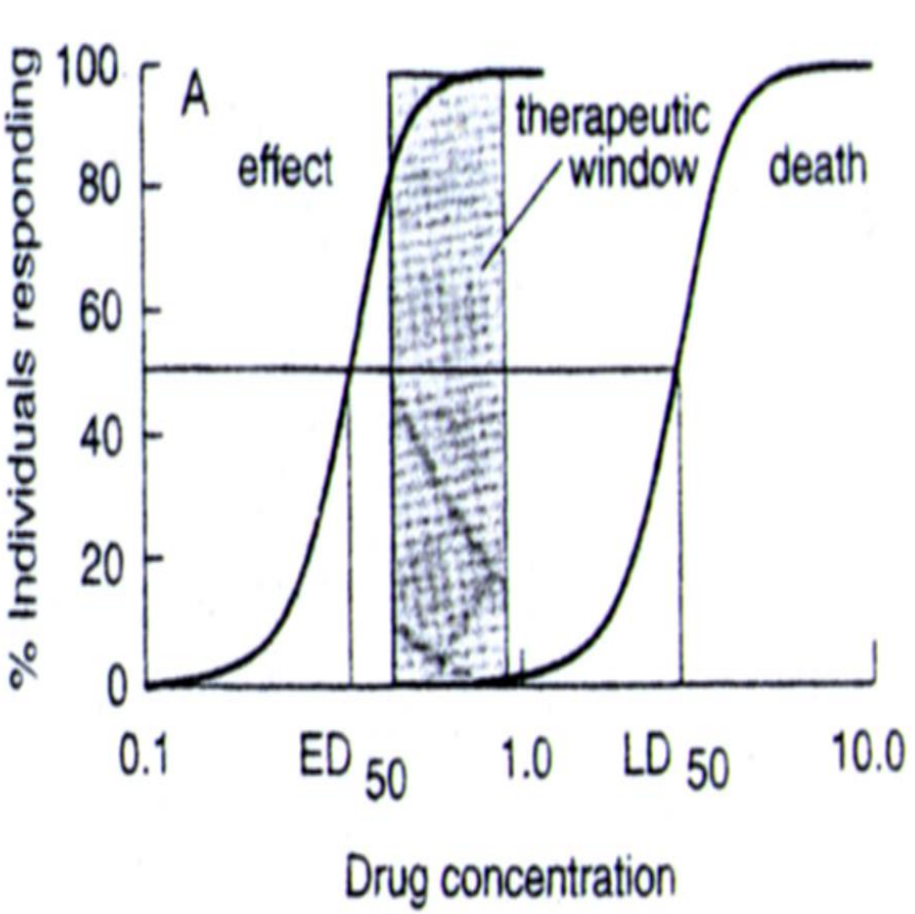
The therapeutic index is the ratio of the toxic or lethal dose LD_{50} of a drug to produce a toxic or lethal effect to the ED50 to produce a therapeutic effect

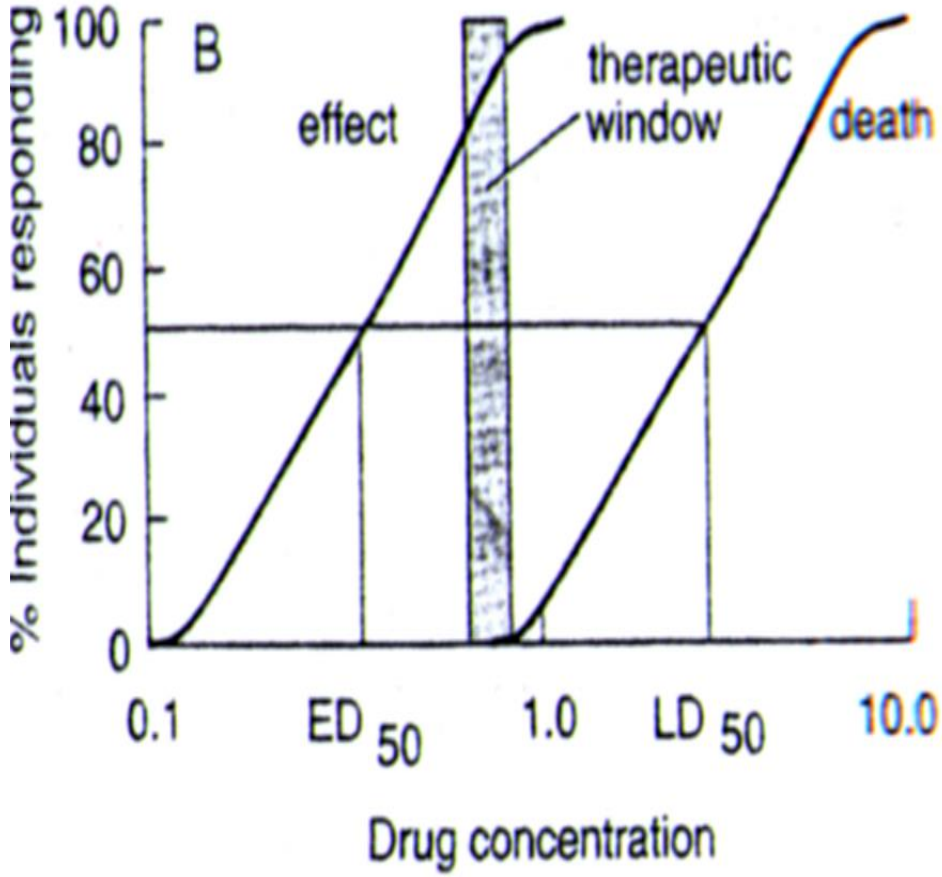
$TI = LD_{50} / ED_{50}$

LD50 = lethal dose: the concentration of drug that gives lethal effect in 50% of the cases.

ED50 = the concentration of drug that gives a therapeutic effect in 50% of the case.

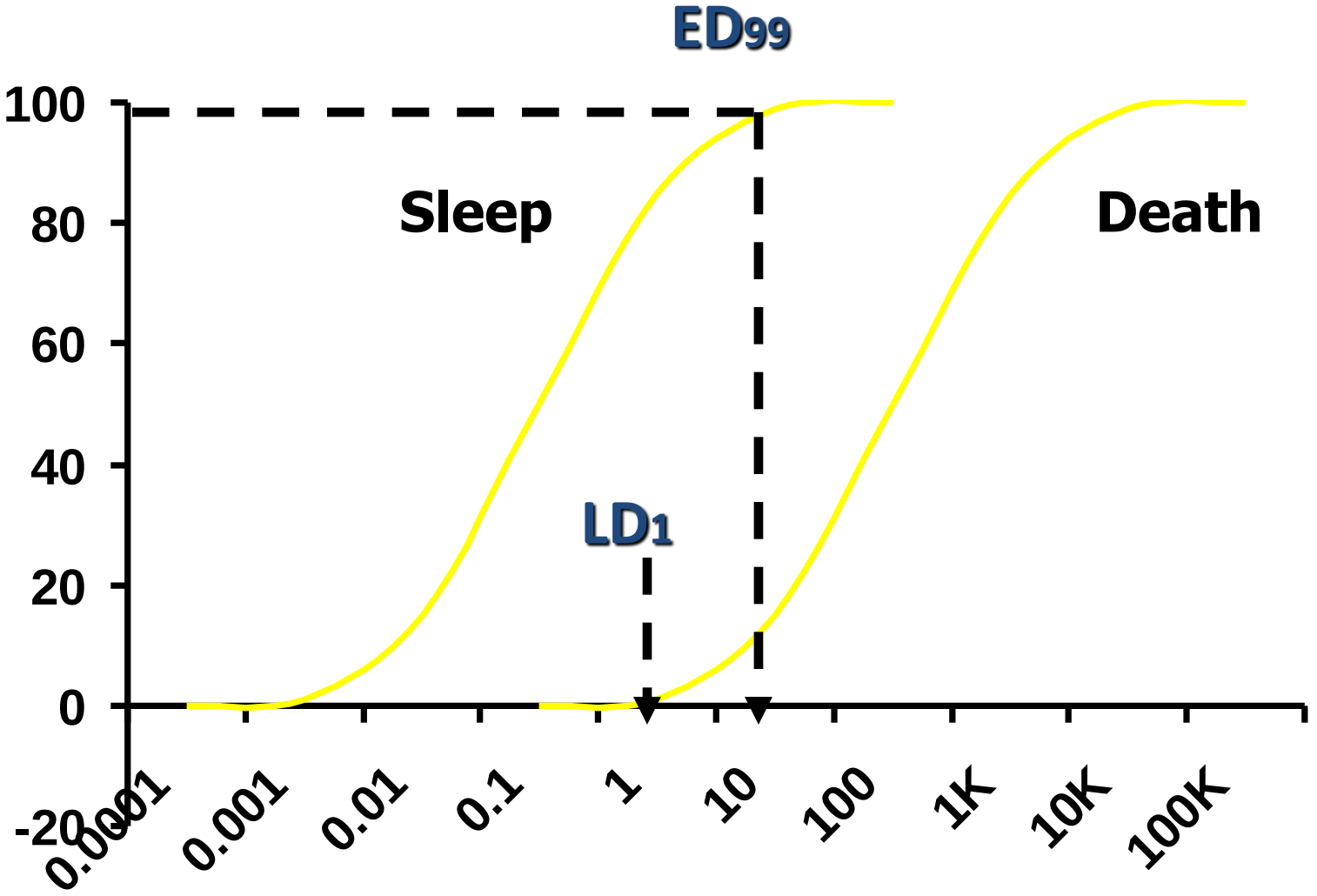
- **Drugs with high therapeutic index have wide safety margin**
- Drugs with low therapeutic index have **narrow safety margin**



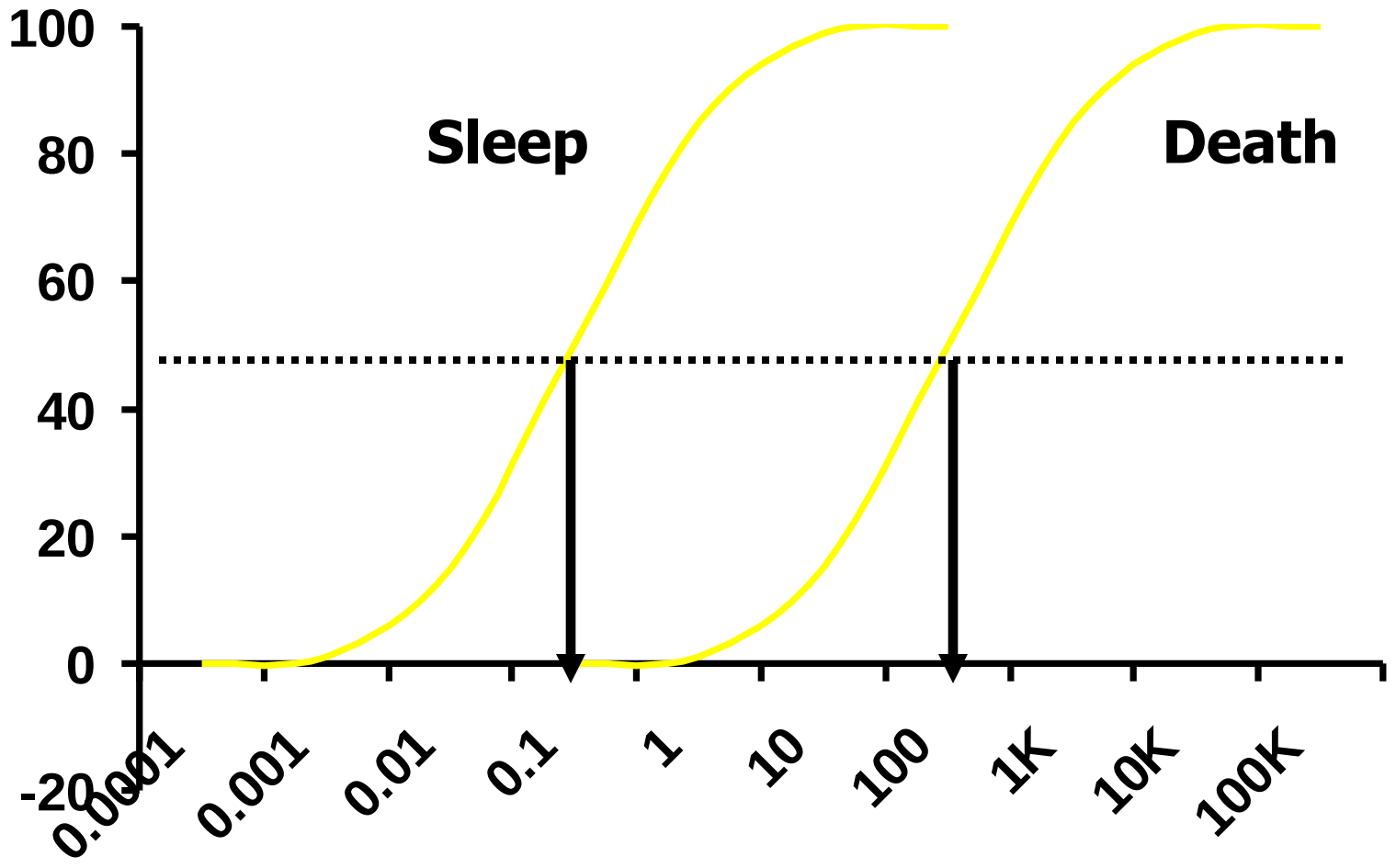


A and B: to have same TI, difference slope

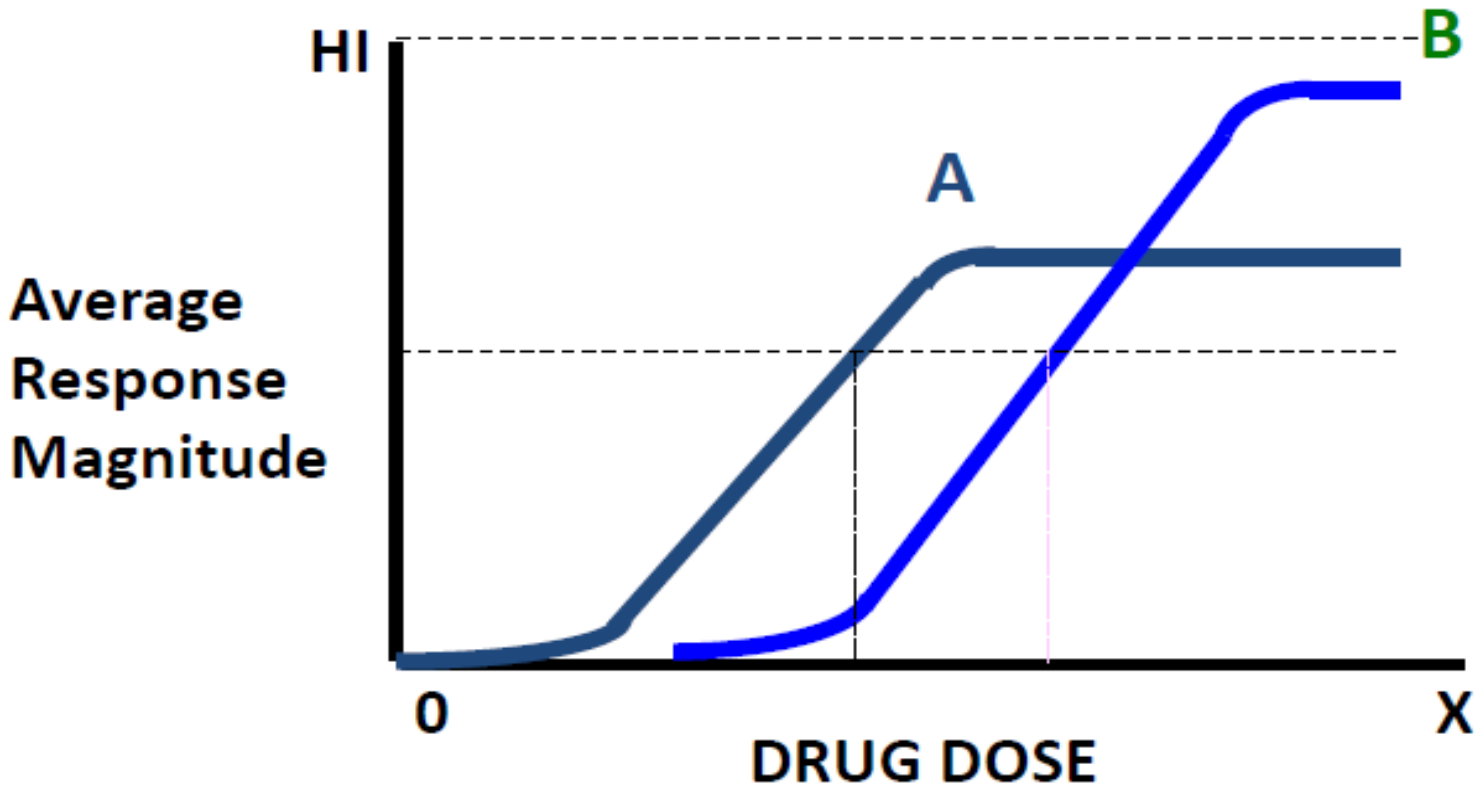
Safety index: LD_1/ED_{99}



Therapeutic index: LD_{50}/ED_{50}

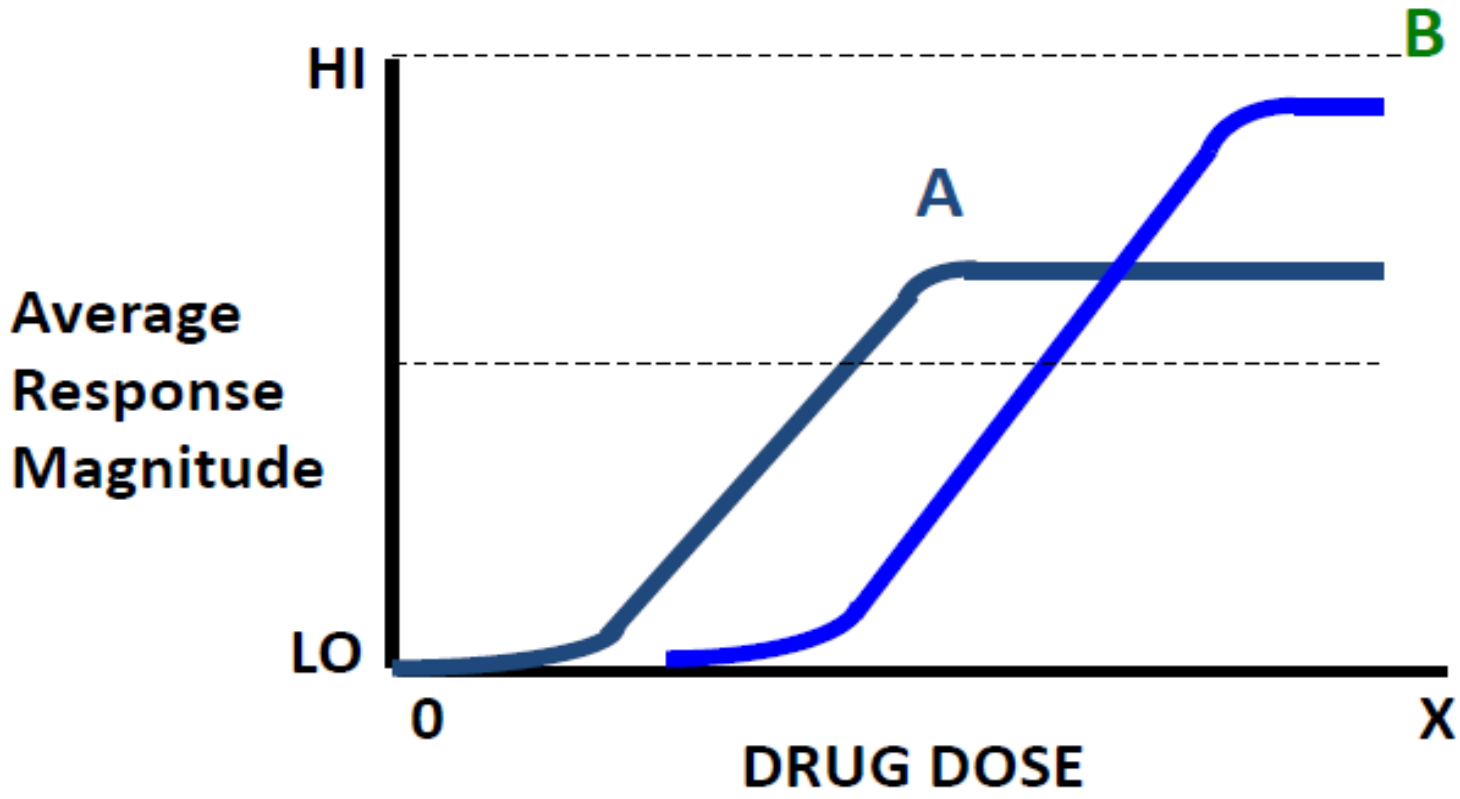


Potency



- A is more potent than B

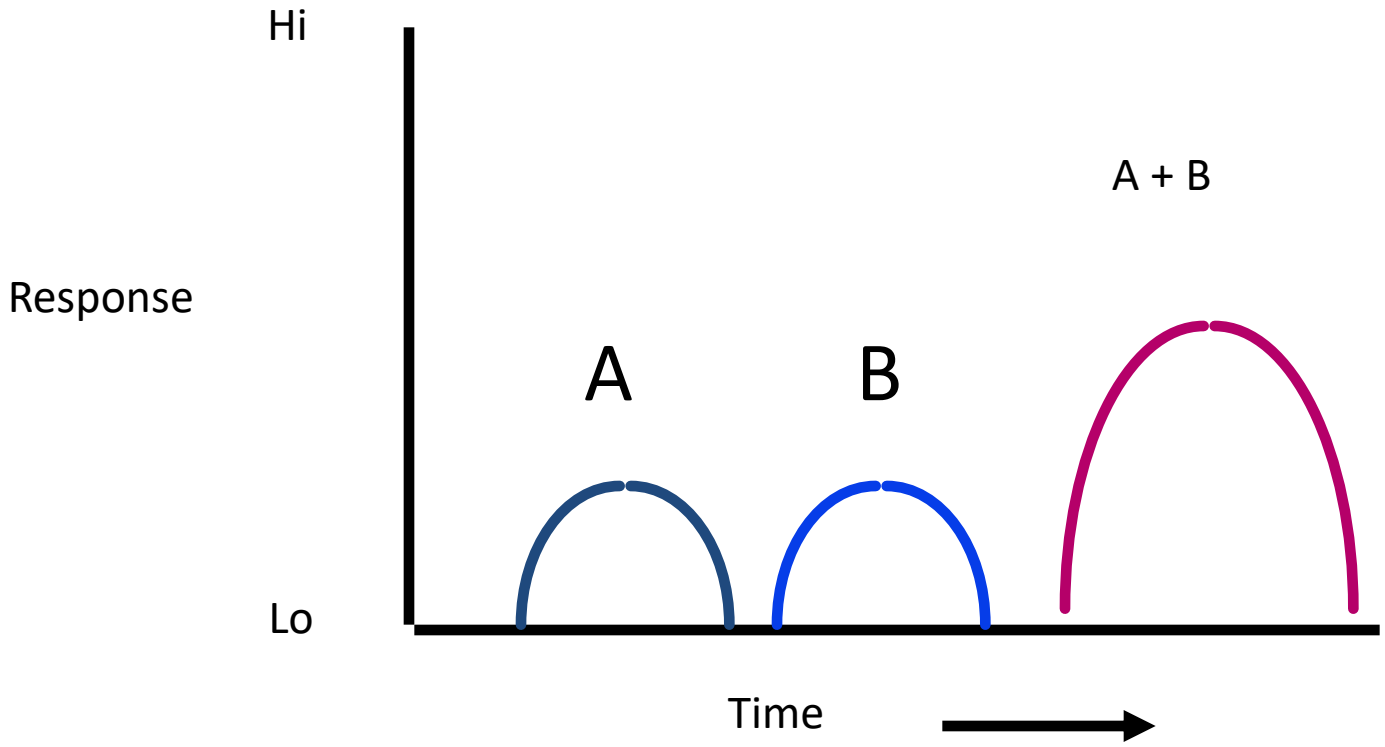
Maximum Efficacy



- B has greater max efficacy than A

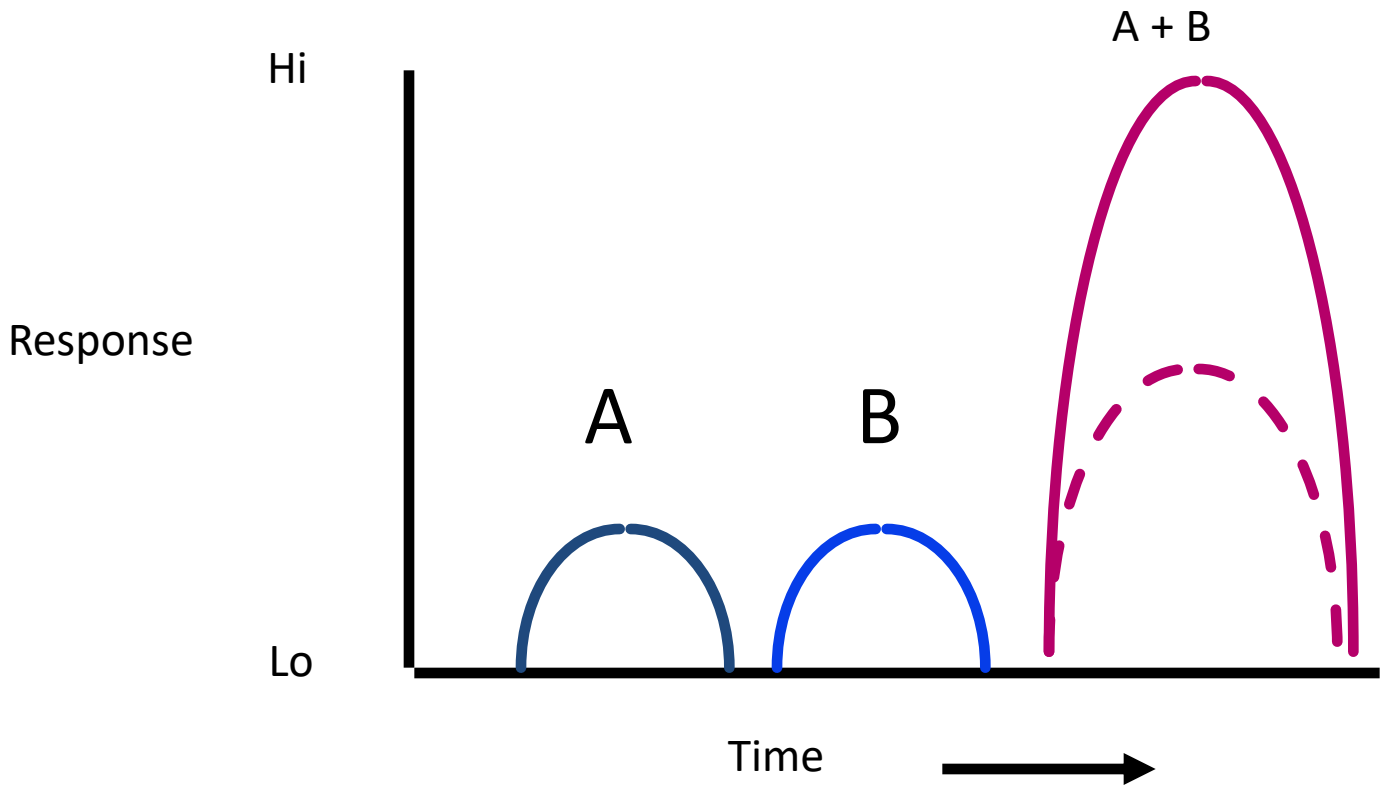
Drug-drug Interactions

Additive Effects



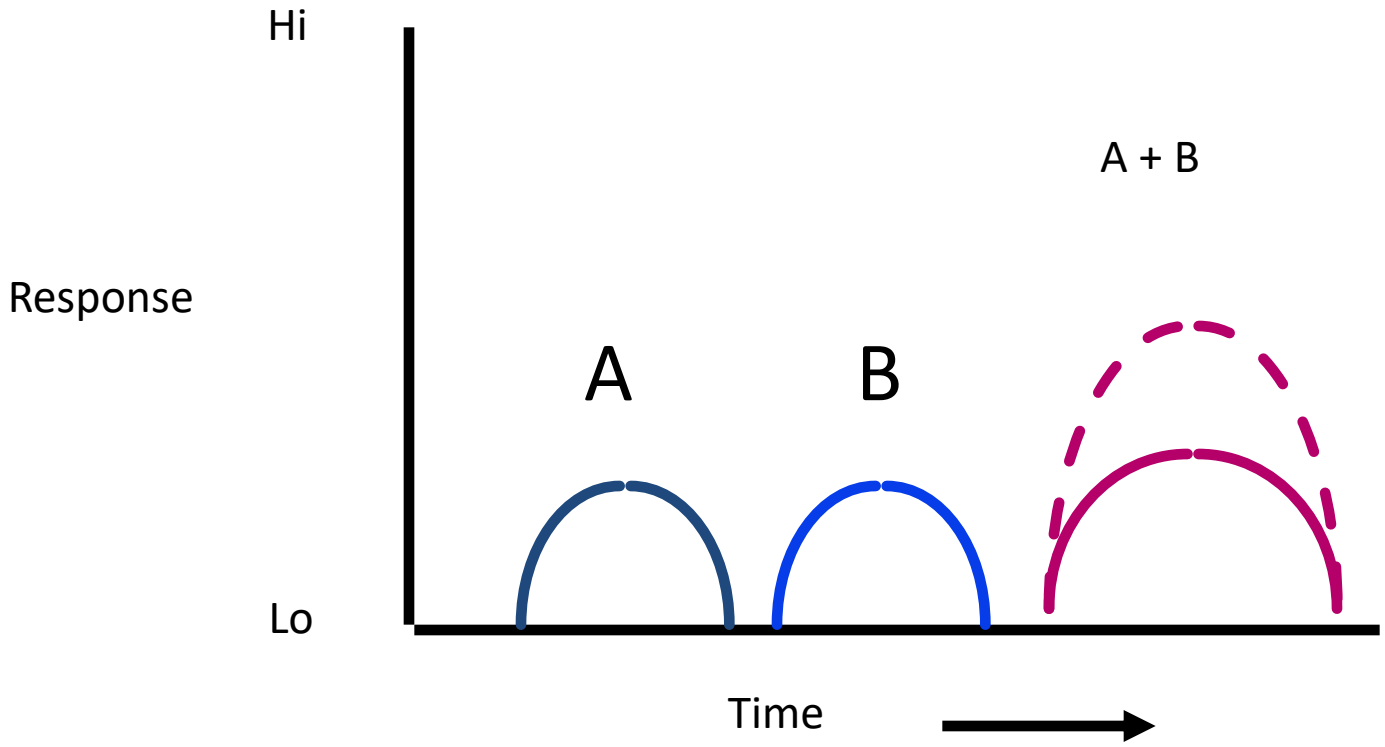
The effect of two chemicals is equal to the sum of the effect of the two chemicals taken separately, eg., aspirin and motrin.

Synergistic Effects



The effect of two chemicals taken together is greater than the sum of their separate effect at the same doses, e.g., alcohol and other drugs

Antagonistic Effects



The effect of two chemicals taken together is less than the sum of their separate effect at the same doses

- **Addictive Effect**
  - An effect in which two substances or actions used in combination produce a total effect the same as the sum of the individual effects ($E_{AB} = E_A + E_B$)
- **Synergistic Effect**
  - The use of two or more drugs that produce a **greater** effect of one drug used alone. ($E_{AB} > E_A + E_B$)
  - Ex. NSAID added to codeine for pain relief

- **Antagonistic Effect**
  - The use of a second drug reduces the effect of another drug
  - The second drug has an antagonistic effect
  - A second drug may bind to the same receptor as the first drug, thus preventing the agonist response. (1+1=0)

Clinical Types of Drug Antagonism

1- **Pharmacological antagonism** When the antagonist competes with the agonist for the specific receptor, combines with the receptor, and prevents the action of the agonist. The antagonist has no intrinsic activity (e.g. diphenhydramine antagonises the action of the endogenous histamine on the specific histamine receptor level as in the treatment of anaphylactic shock). This type of antagonism is further subdivided into:

A- **Reversible antagonism** This may be demonstrated with many antagonists. Reversible (competitive) antagonists Increasing the concentration of the agonist can fully overcome the inhibition by the antagonist (e.g. atropine and tubocurarine antagonising the actions of acetylcholine at muscarinic and nicotinic receptors respectively).

B- Irreversible antagonism When increasing the concentration of the agonist will never fully overcome the inhibition. This is probably due to receptor inactivation (e.g. phenoxybenzamine at a-receptors in blood vessels). Irreversible antagonism can also be observed on the activity of the appropriate enzymes; recovery of the enzyme activity depends on the formation of new enzymes.

selected list of clinically important irreversible antagonists

Drug	Site
Phenoxybenzamine	α-adrenoceptors
DFP (organophosphate)	Cholinesterase
Aspirin	Prostaglandin G/H synthase
Tranylcypromine & phenelzine*	MAO (non-selective)
Deprenyl (selegiline)	MAO-B
Omeprazole	H^+,K^+-ATPase
Vigabatrin	GABA transaminase
Clopidogrel	ADP receptors
Alloxanthine (oxypurinol)	Xanthine oxidase
Clavulanic acid	Constitutive β-lactamase

. Physiologic (functional) antagonist

Physiologic antagonism occurs when the actions of two agonists working at two different receptor types have opposing (antagonizing) actions

Example 1: Histamine acts at H_1 receptors on bronchial smooth muscle to cause bronchoconstriction, whereas adrenaline is an agonist at the β_2 receptors bronchial smooth muscle, which causes bronchodilation.
Example 2: histamine acts on receptors of the parietal cells of the gastric mucosa to stimulate acid secretion, while omeprazole blocks this effect by inhibiting the proton pump

. Chemical antagonist

antagonism occurs when two substances combine in solution → the active drug is lost

Example : Chelating agents (e.g., dimercaprol) that bind heavy metals, and thus reduce their toxicity

- **Antagonistic Effect**
  - **The use of a second drug reduces the effect of another drug**
  - **The second drug has an antagonistic effect**
  - **A second drug may bind to the same receptor as the first drug, thus preventing the agonist response**

Thank you