Al-Mustaqbal University

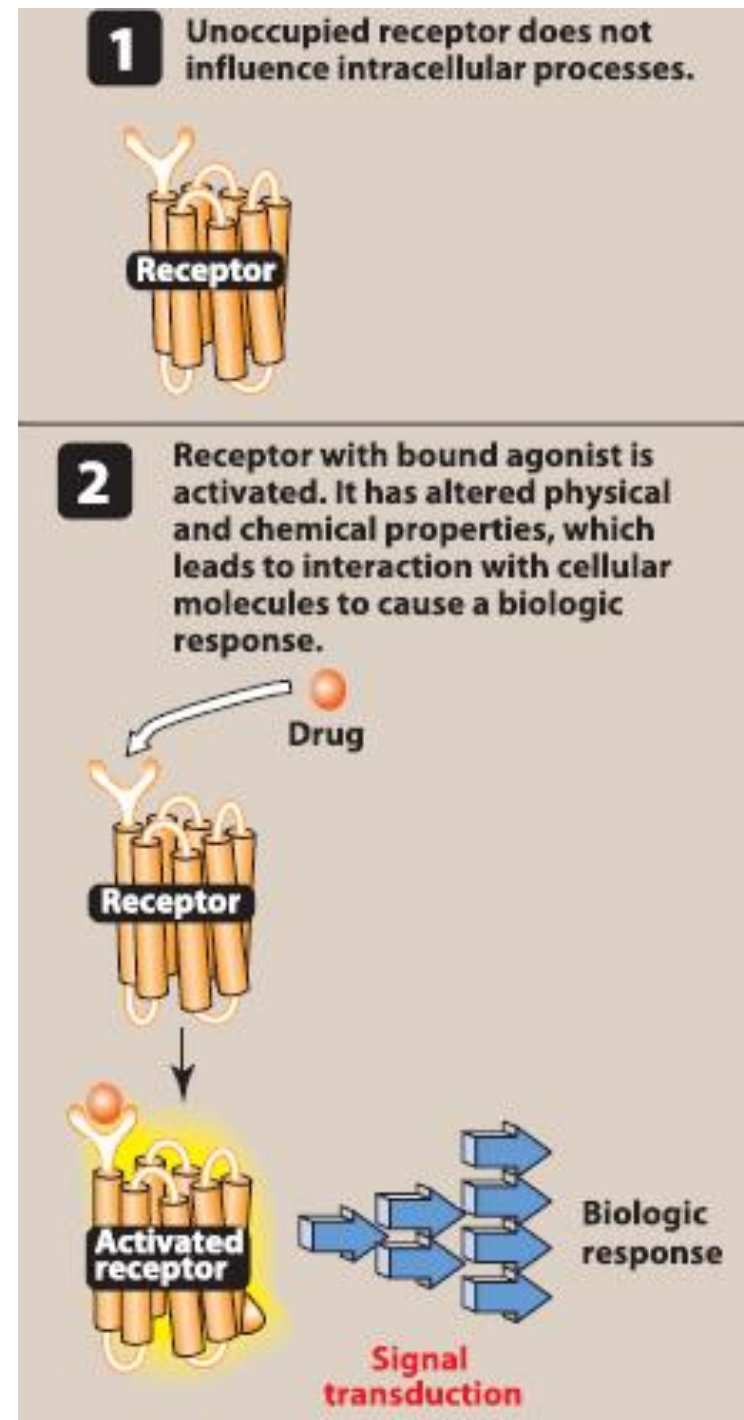**Pharmacology I**
3ʳᵈ stage
Drug-Receptor Interactions and Pharmacodynamics
Dr. Hasanain Owadh

Drug-Receptor Interactions and Pharmacodynamics

Pharmacodynamics describes the actions of a drug on the body.

Most drugs exert effects, both beneficial and harmful, by interacting with specialized target macromolecules called receptors, which are present on or in the cell.

1 Unoccupied receptor does not influence intracellular processes.

Receptor

2 Receptor with bound agonist is activated. It has altered physical and chemical properties, which leads to interaction with cellular molecules to cause a biologic response.

Drug

Receptor

Activated receptor

Biologic response
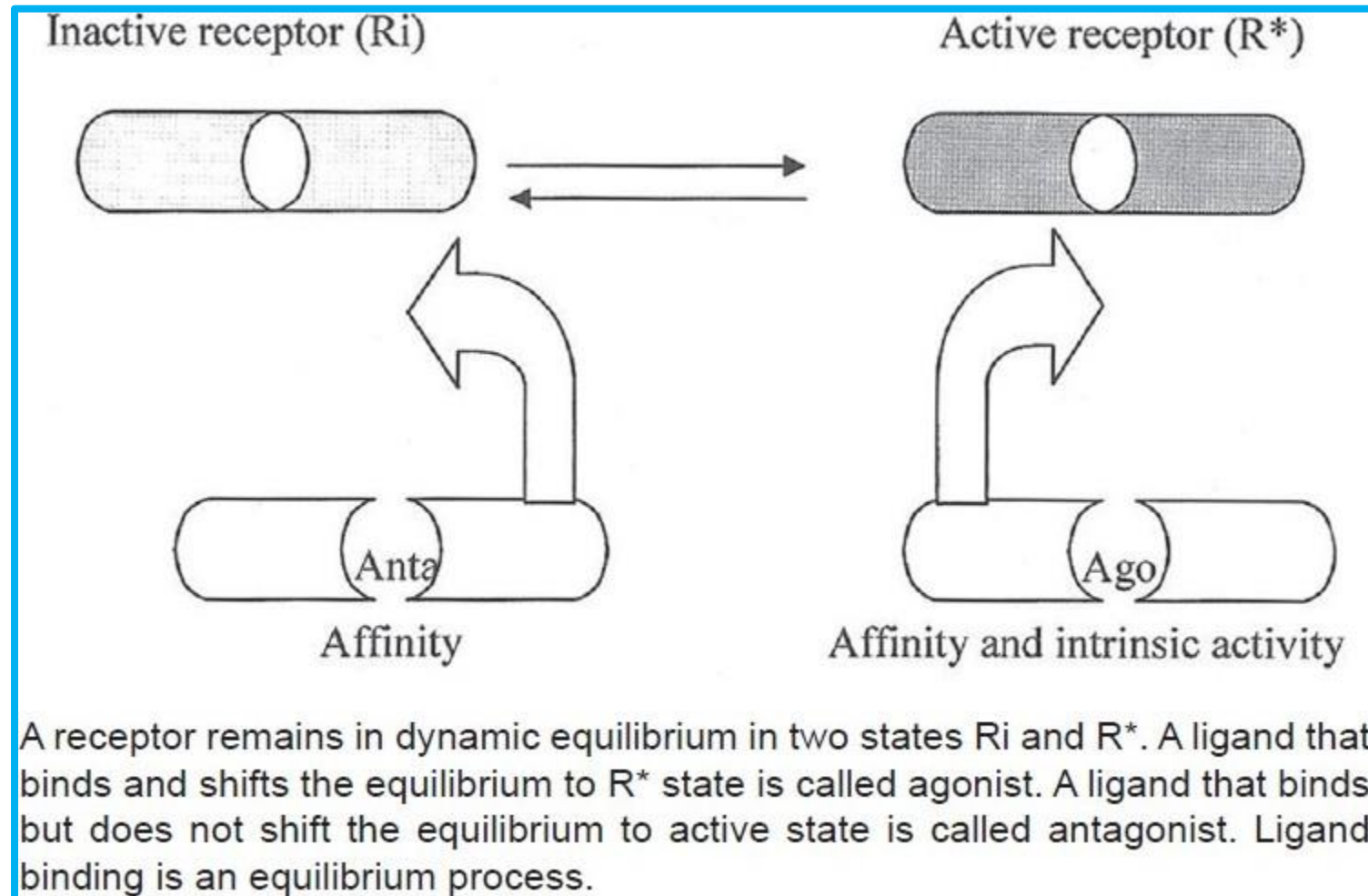
Signal transduction

Signal Transduction

Drugs act as signals, and receptors act as signal detectors.

A drug is termed an agonist if it binds to a site on a receptor protein and activates it to initiate a cellular response.

It is important to know that not all drugs exert effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing stomach upset.
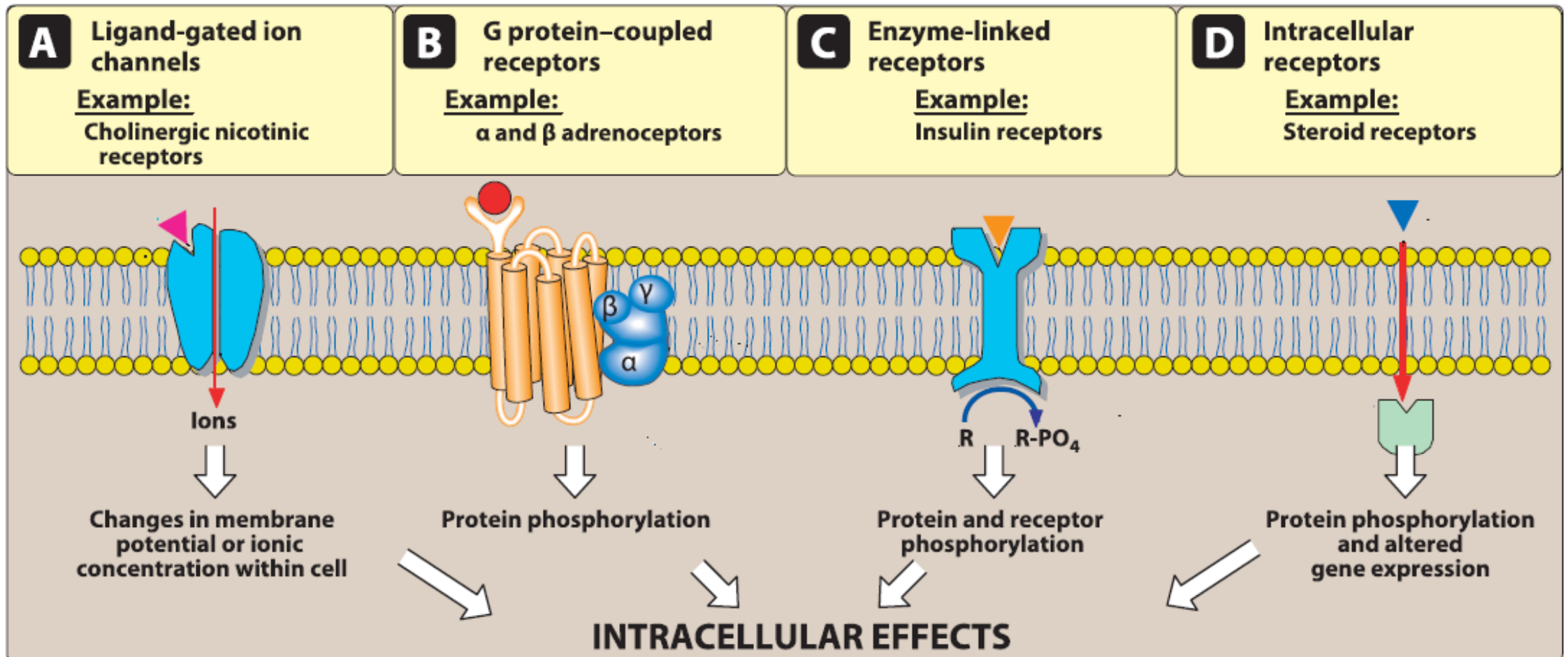
Receptor states

Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium

Inactive receptor (Ri) Active receptor (R*)

Anta Ago

Affinity Affinity and intrinsic activity

A receptor remains in dynamic equilibrium in two states Ri and R*. A ligand that binds and shifts the equilibrium to R* state is called agonist. A ligand that binds but does not shift the equilibrium to active state is called antagonist. Ligand binding is an equilibrium process.

Major receptor families

A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response. the richest sources of receptors are membrane bound proteins that transduce extracellular signals into intracellular responses.

A Ligand-gated ion channels	**B** G protein–coupled receptors	**C** Enzyme-linked receptors	**D** Intracellular receptors
Example: Cholinergic nicotinic receptors	Example: α and β adrenoceptors	Example: Insulin receptors	Example: Steroid receptors

Ions

β γ α

R   R-PO$_4$

Changes in membrane potential or ionic concentration within cell

Protein phosphorylation

Protein and receptor phosphorylation

Protein phosphorylation and altered gene expression

INTRACELLULAR EFFECTS

1. Transmembrane ligand-gated ion channels: The extracellular portion of ligand-gated ion channels contains the drug-binding site.

This site regulates the opening of the pore through which ions can flow across cell membranes. The action usually last milliseconds.

For example, stimulation of the nicotinic receptor by acetylcholine opens a channel that allows sodium influx and potassium outflux across the cell membranes of neurons or muscle cells.

On the other hand, agonist stimulation of the A subtype of the γ-aminobutyric acid (GABA) receptor increases chloride influx, resulting in hyperpolarization.

Drug-binding sites are also found on many voltage-gated ion channels where they can regulate channel function example, local anesthetics, inhibiting sodium influx and decreasing neuronal conduction..

2. Transmembrane G protein-coupled receptors: The extracellular portion of this receptor contains the ligand-binding site, and the intracellular portion interacts (when activated) with a G protein.

Binding to extracellular portion lead to intracellular portion become free to interact with specific cellular effectors, usually an enzyme or an ion channel, that cause further actions within the cell.

These responses usually last several seconds to minutes.

Often, the activated effectors produce "second messenger" molecules that further activate other effectors in the cell, causing a signal cascade effect.

 1- cyclic adenosine monophosphate (cAMP).
 2- inositol1 ,4,5-trisphosphate (IP3)
 3- diacylglycerol (DAG).
 4- Ca ion.

3. Enzyme-linked receptors: This family of receptors undergoes conformational changes when activated by a ligand, resulting in increased intracellular enzyme activity.

This response lasts for minutes to hours.

The most common enzyme-linked receptors (for example, growth factors and insulin) possess tyrosine kinase activity.

- - G protein-coupled receptors ….
- a- haveα subunit binds guanosine triphosphate (GTP),
- b- have β subunits anchor the G protein in the cell membrane.
- c- have γ subunits anchor the G protein in the cell membrane.
- d- all of the above
- e- none of the above

Q- all the following are second messengers except:

o cyclic adenosine monophosphate (cAMP) .

o inositol1 ,4,5-trisphosphate (IP3)

o diacylglycerol (DAG).

o Ca ion.

o G protein-coupled receptors.

- 4- all the following are enzyme-linked receptors except …
- a- insulin (tyrosine kinase) receptor
- b- platelet-derived growth factor (tyrosine kinase) receptor
- c- nicotinic receptor
- d- atrial natriuretic peptide (tyrosine kinase) receptor
- e- epidermal growth factor (tyrosine kinase) receptor
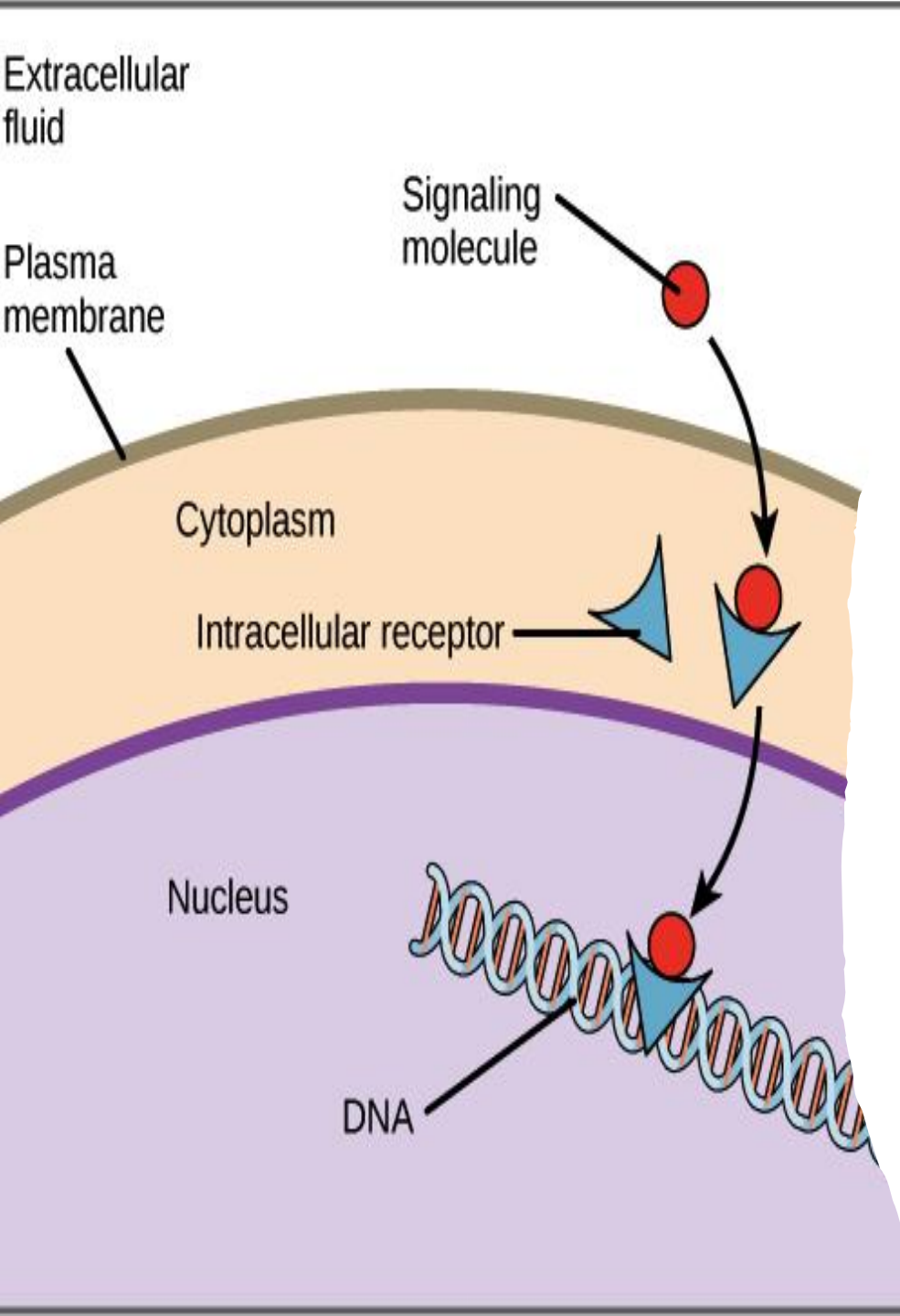
- 4. **Intracellular receptors:** The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand (for example, steroid hormones) must have sufficient lipid solubility to diffuse into the cell to interact with the receptor.

- Activate intracellular receptors takes hours to days to occur.

Which family do receptors belong to when they are found inside cells, interacting with hydrophobic ligands?

A) Ligand-gated ion channels
B) G protein-coupled receptors
C) Enzyme-linked receptors
D) Intracellular receptors
E) Structural proteins

Q. Which type of drugs generally interacts with intracellular receptors?

A) Hydrophilic drugs
B) Hydrophobic drugs
C) Enzymatic drugs
D) Weak basic drugs
E) weak acidic drugs

D. Characteristics of signal transduction
Signal transduction has two important features:
1) The ability to amplify small signals (intensity and duration).

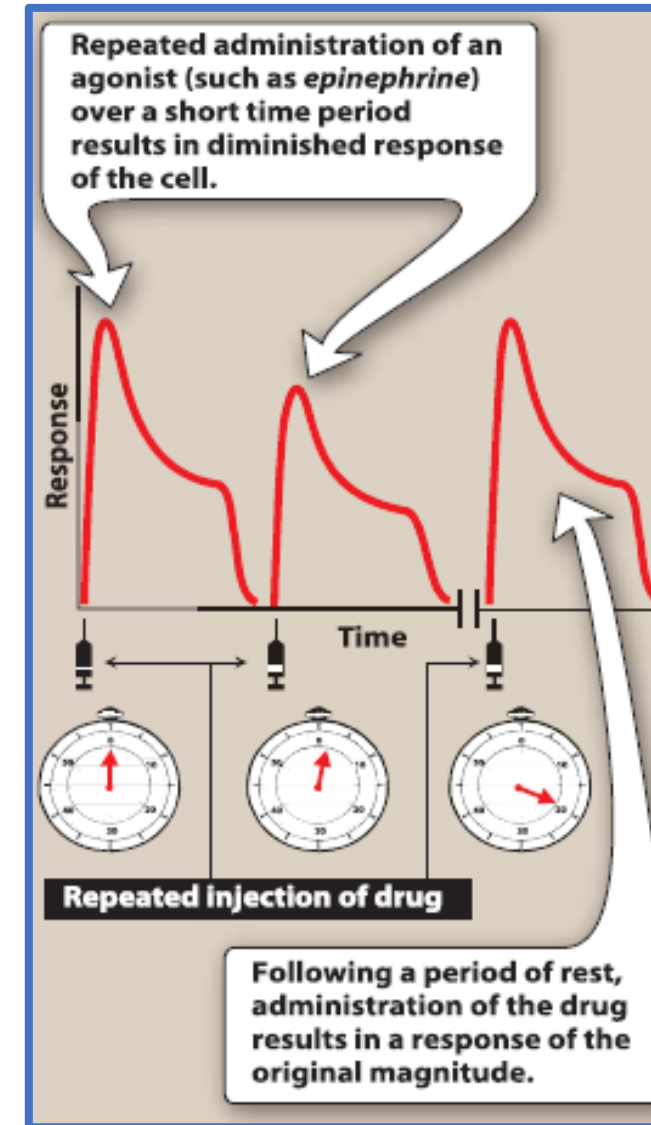Systems that exhibit this behavior are said to have spare receptors.

About 99% of insulin (enzyme-linked) receptors are "spare" providing an immense functional reserve that ensures that adequate mounts of glucose enter the cell.
And 5% to 10% of the total β-adrenoceptors (G protein-linked receptor) in the heart are spare.

2) Desensitization and down-regulation of receptors:

The receptor may become desensitized due to too much agonist stimulation, resulting in a diminished response. This phenomenon, called tachyphylaxis.

Repeated exposure of a receptor to an antagonist, on the other hand, results in up-regulation of receptors, in which receptor reserves are inserted into the membrane, increasing the number of receptors available.

Repeated administration of an agonist (such as *epinephrine*) over a short time period results in diminished response of the cell.

Response

Time

Repeated injection of drug

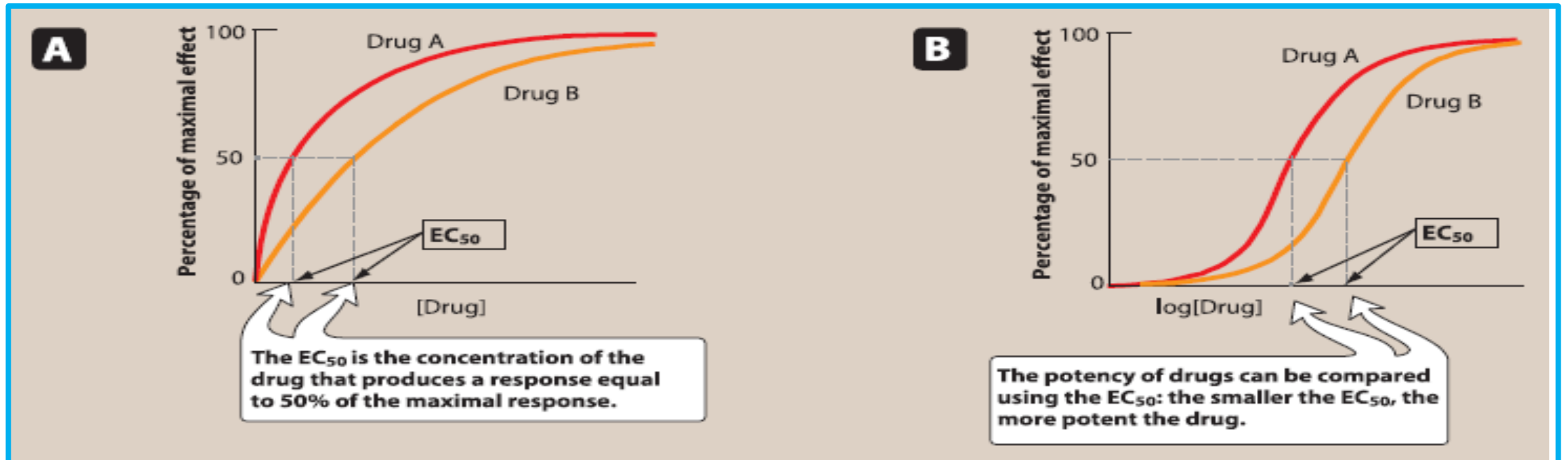Following a period of rest, administration of the drug results in a response of the original magnitude.

DOSE-RESPONSE RELATIONSHIPS

Agonist drugs mimic the action of the endogenous ligand for the receptor
As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect).

1. Potency: Potency is a measure of the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect (EC_{50}) is often used to determine potency.

A: The EC_{50} is the concentration of the drug that produces a response equal to 50% of the maximal response.

B: The potency of drugs can be compared using the EC_{50}: the smaller the EC_{50}, the more potent the drug.
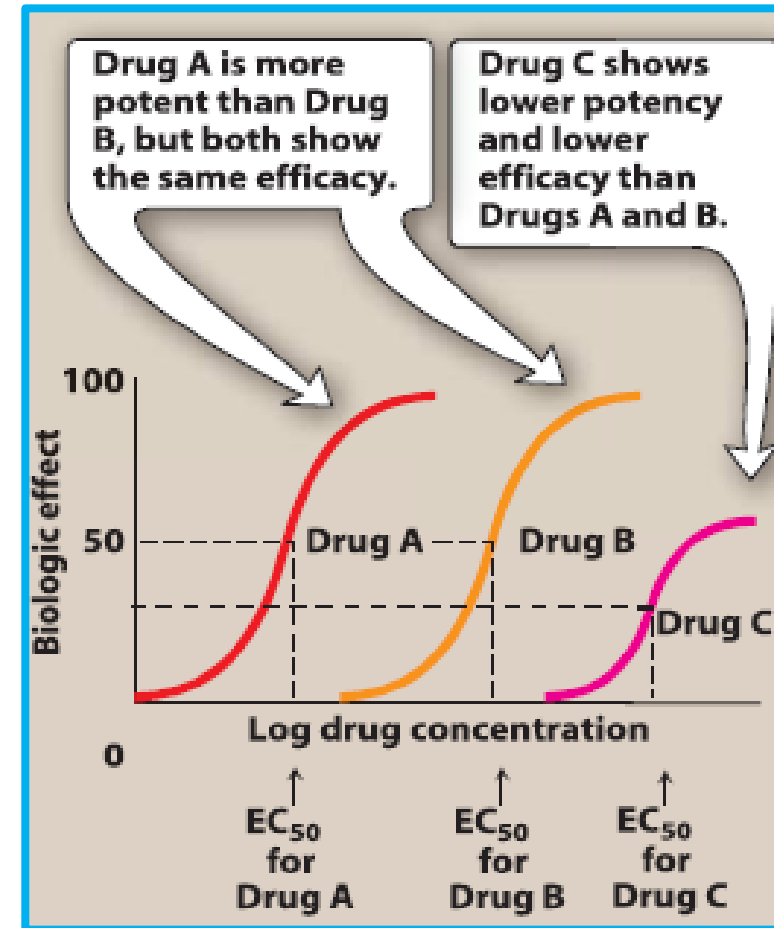
- The therapeutic dose range for candesartan is 4 to 32 mg, as compared to 75 to 300 mg for irbesartan. Therefore, candesartan is
- a- more potent
- b- less potent
- c- equal potency
- d- EC50 of irbesartan less than EC50 of candesartan
- e- none of the above

2. Efficacy: Efficacy is the magnitude of response a drug causes when it interacts with a receptor.

Maximal efficacy of a drug (Emax) assumes that the drug occupies all receptors, and no increase in response is observed in response to higher concentrations of drug.

Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent.

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.

Q- when EC_{50} of drug A less than EC_{50} of drug B this means drug A:

o more potent.

o less potent.

o equal potency.

o less efficacy.

o more efficacy.
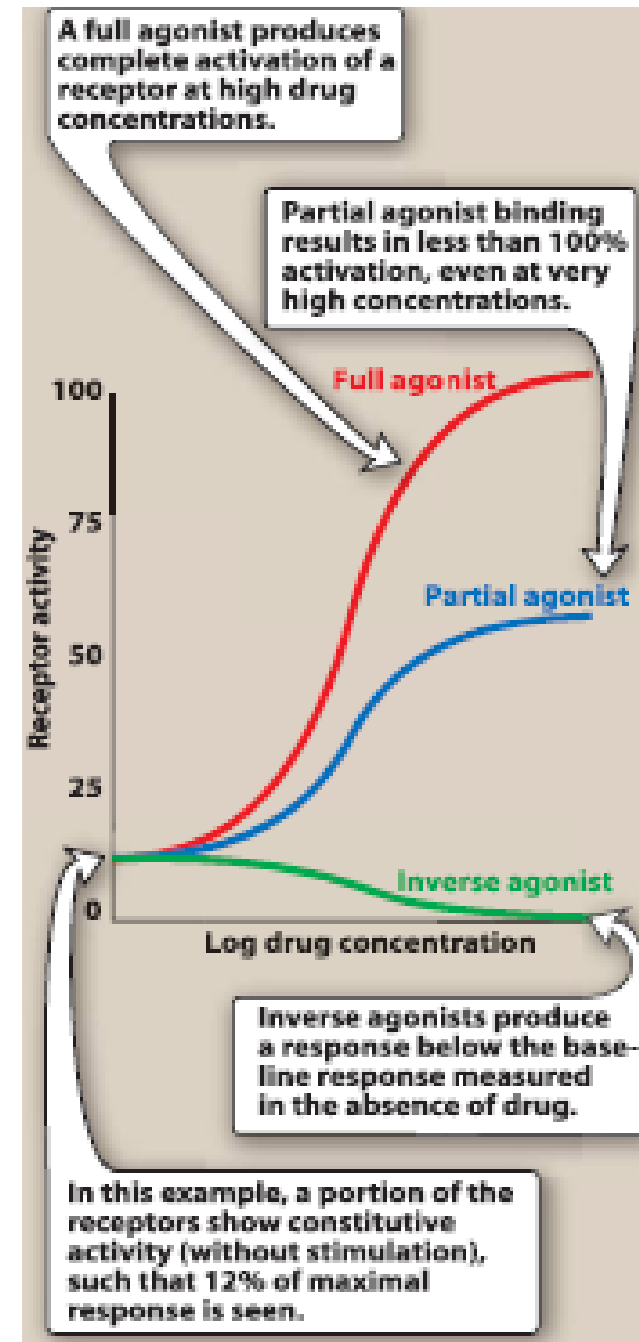
Intrinsic Activity:

An agonist binds to a receptor and produces a biologic response based on the concentration of the agonist and the fraction of activated receptors.

The intrinsic activity of a drug determines its ability to fully or partially activate the receptors. Drugs may be categorized according to their intrinsic activity and resulting Emax values.

Full agonists

If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is a full agonist.

All full agonists for a receptor population should produce the same E_{max}. For example, phenylephrine is a full agonist at α_1-adrenoceptors, because it produces the same E_{max} as the endogenous ligand, norepinephrine.

A full agonist produces complete activation of a receptor at high drug concentrations.

Partial agonist binding results in less than 100% activation, even at very high concentrations.

Full agonist

Partial agonist

Inverse agonist

Receptor activity

100

75

50

25

0

Log drug concentration

Inverse agonists produce a response below the base-line response measured in the absence of drug.

In this example, a portion of the receptors show constitutive activity (without stimulation), such that 12% of maximal response is seen.

Partial agonists have intrinsic activities greater than zero but less than one. Even when all the receptors are occupied, partial agonists cannot produce the same Emax as a full agonist.

This potential of partial agonists to act as both an agonist and antagonist may have therapeutic utility.
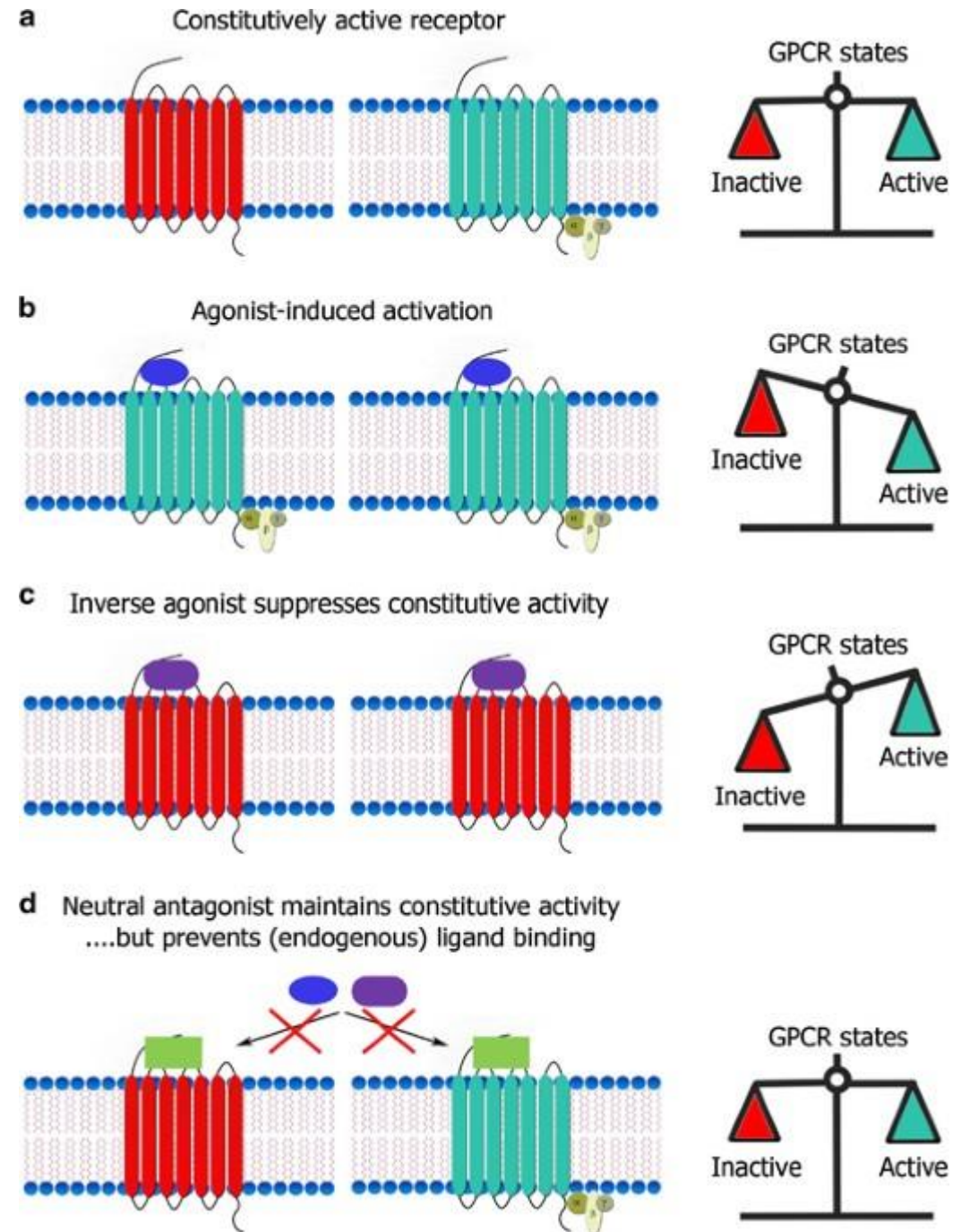
For example, aripiprazole, an atypical antipsychotic, is a partial agonist at selected dopamine receptors. Overactive dopaminergic pathways tend to be inhibited by aripiprazole, whereas underactive pathways are stimulated. This might explain the ability of aripiprazole to improve symptoms of schizophrenia, with a small risk of causing extrapyramidal adverse effects. explain

Inverse agonists

Inverse agonists, unlike full agonists, stabilize the inactive R form and cause R* to convert to R.

This decreases the number of activated receptors to below that observed in the absence of drug. Thus, inverse agonists have an intrinsic activity less than zero.

a Constitutively active receptor

GPCR states

Inactive   Active

b Agonist-induced activation

GPCR states

Inactive   Active

c Inverse agonist suppresses constitutive activity

GPCR states

Inactive   Active

d Neutral antagonist maintains constitutive activity ....but prevents (endogenous) ligand binding

GPCR states

Inactive   Active

Antagonists

Antagonists bind to a receptor with high affinity but possess zero intrinsic activity.

Antagonism may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

1- Competitive antagonists:

A competitive antagonist interferes with an agonist binding to its receptor and maintains the receptor in its inactive state.
However, increasing the concentration of agonist relative to antagonist can overcome this inhibition.
Thus, competitive antagonists characteristically shift the agonist dose response curve to the right (increased EC_{50}) without affecting E_{max}.

2. Irreversible antagonists: Irreversible antagonists bind covalently to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist.

In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists.

3. Allosteric antagonists: An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist.

Irreversible antagonists and allosteric antagonists are both considered noncompetitive antagonists.

4. Functional antagonism: An antagonist may act at a completely separate receptor, initiating effects that are functionally opposite those of the agonist.

A classic example is the functional antagonism by epinephrine to histamine-induced bronchoconstriction.

Histamine binds to H_1 histamine receptors on bronchial smooth muscle, causing bronchoconstriction of the bronchial tree.

Epinephrine is an agonist at β_2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax. This functional antagonism is also known as "physiologic antagonism."

Q- In the presence of picrotoxin, diazepam is less efficacious at causing sedation, regardless of the dose. Picrotoxin has no sedative effect, even at the highest dose. Which of the following is correct regarding these agents?

o Picrotoxin is a competitive antagonist.

o Picrotoxin is a noncompetitive antagonist.

o Diazepam is less efficacious than is picrotoxin.

o Diazepam is less potent than is picrotoxin.

o Diazepam is a competitive antagonist.

Quantal Dose-Response Curve:

Another important dose-response relationship is that between the dose of the drug and the proportion of a population of patients that responds to it.

Quantal dose-response curves are useful for determining doses to which most of the population responds. They have similar shapes as log dose-response curves, and the ED50 is the drug dose that causes a therapeutic response in half of the population.
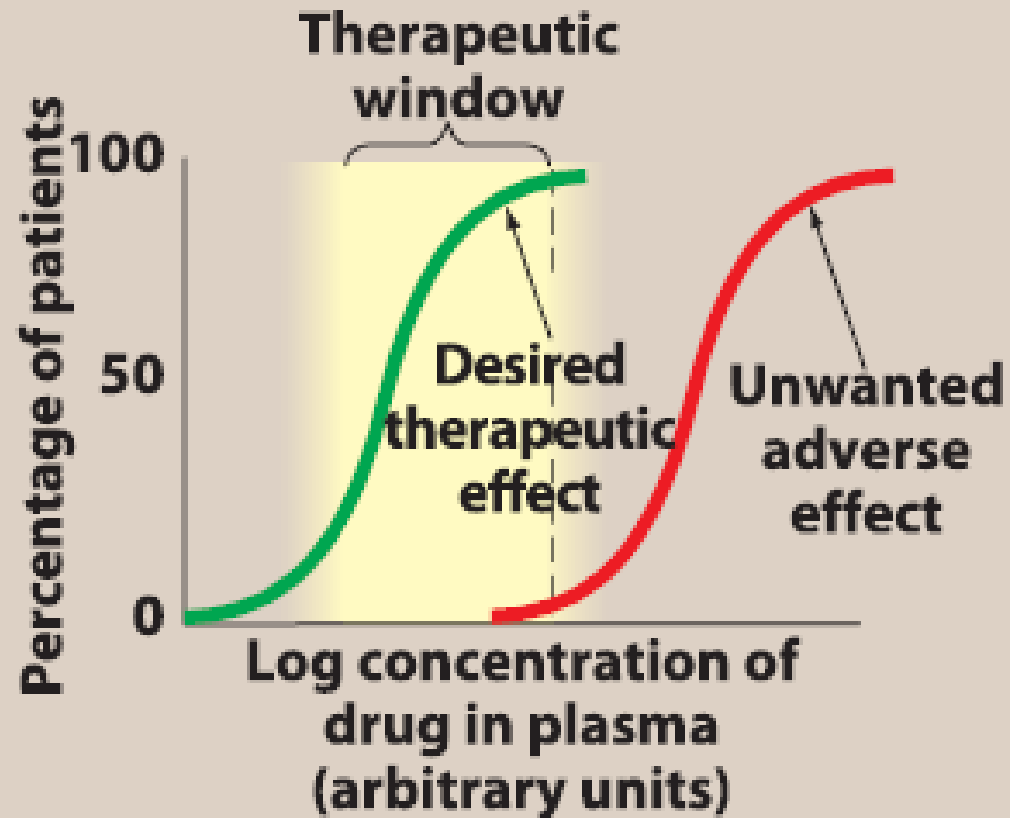
Therapeutic index

The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD_{50}) to the dose that produces a clinically desired or effective response (ED_{50}) in half the population:

$$Tl = TD_{50} / ED_{50}$$

The Tl is a measure of a drug's safety, because a larger value indicates a wide margin between doses that are effective and doses that are toxic.

Warfarin: Small therapeutic index

- B. Clinical usefulness of the therapeutic Index

- The Tl of a drug is determined using drug trials and accumulated clinical experience.

- These usually reveal a range of effective doses and a different (sometimes overlapping) range of toxic doses.

Penicillin (example of a drug with a large therapeutic index):
It is safe and common to give doses in excess of that which is minimally required to achieve a desired response without the risk of adverse effects.

B *Penicillin*: Large therapeutic index
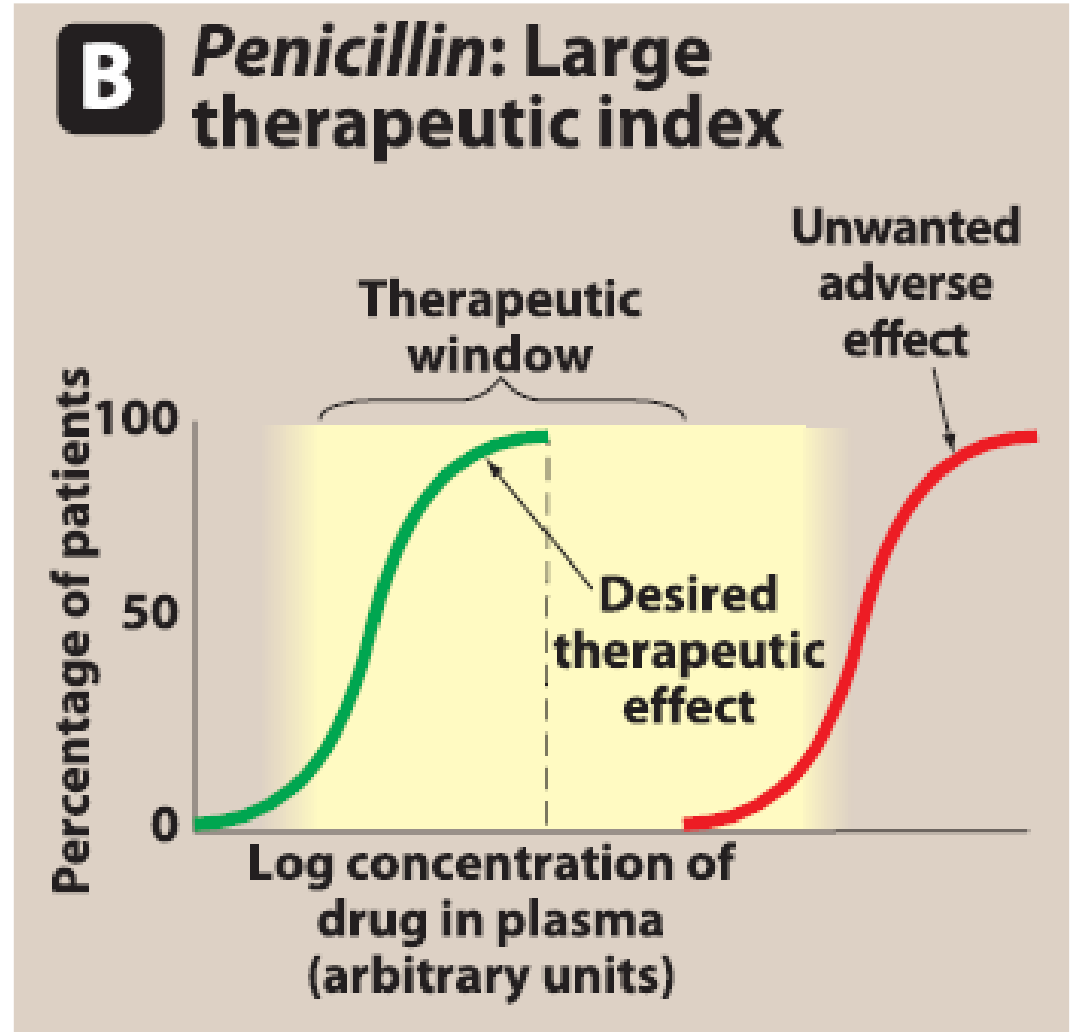
References

Lippincott Illustrated Reviews: Pharmacology. 7TH ed, Wolters Kluwer.

Thank you