Al-Mustaqbal University College

Pharmacology I 3rd stage

Drug-Receptor Interactions and Pharmacodynamics

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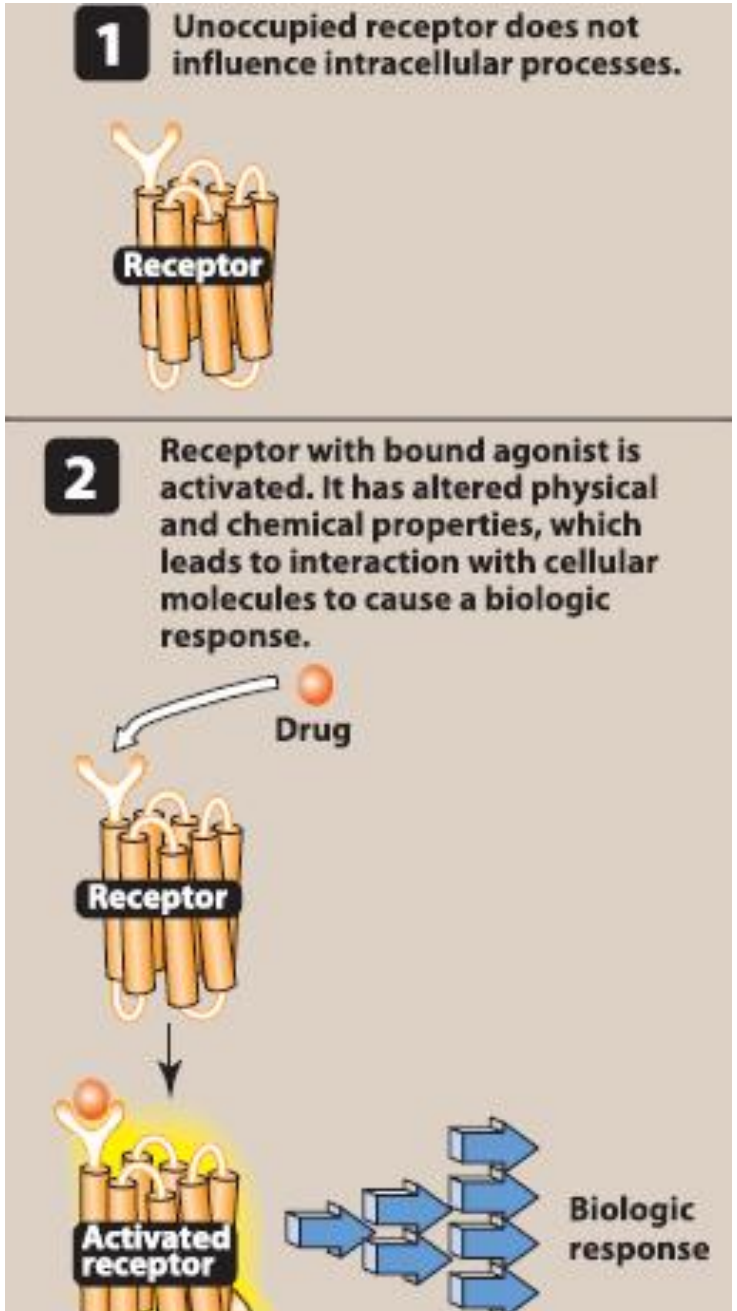
Drug-Receptor Interactions and Pharmacodynamics

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.



Signal Transduction

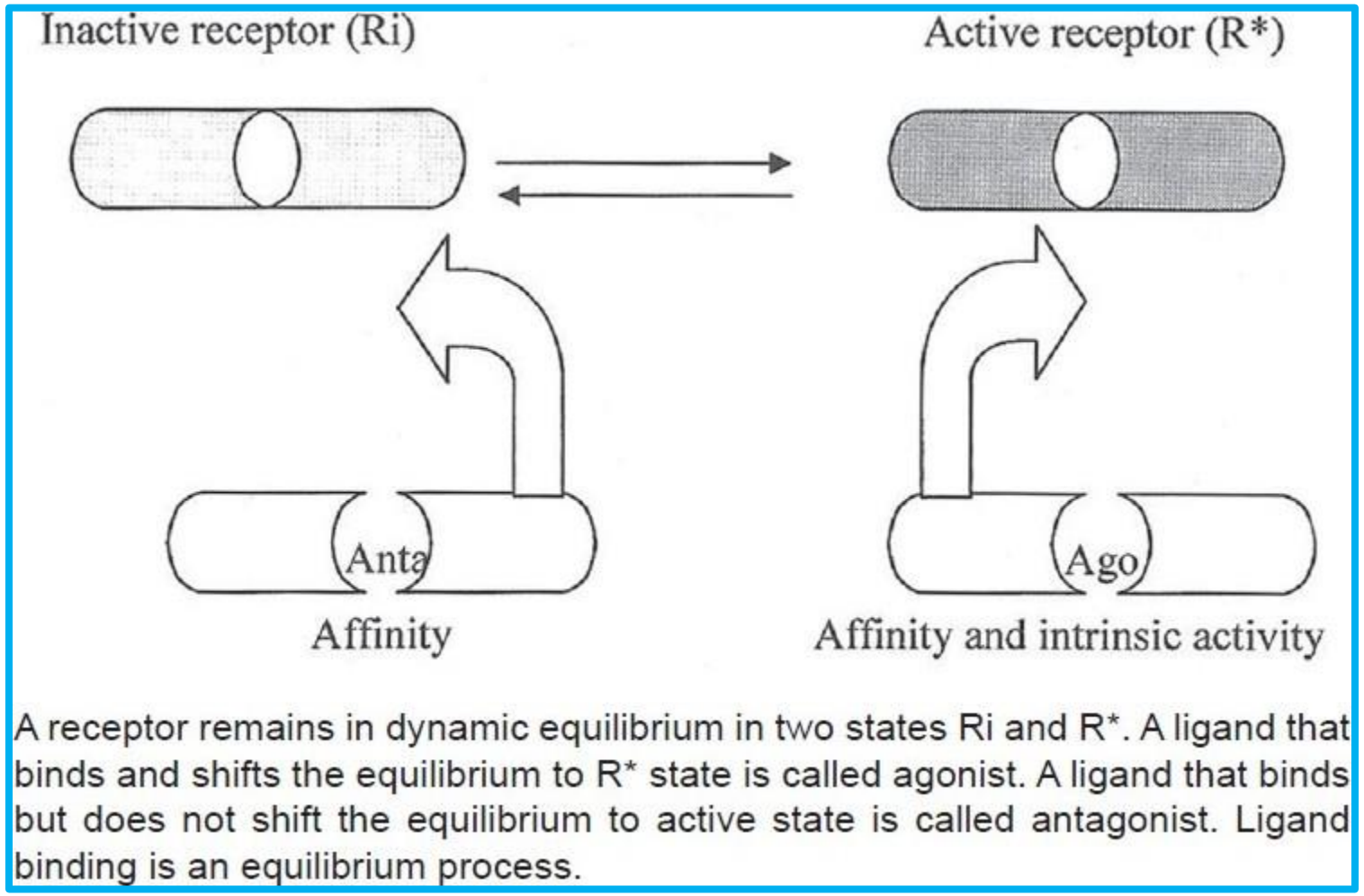
Drugs act as signals, and receptors act as signal detectors.

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

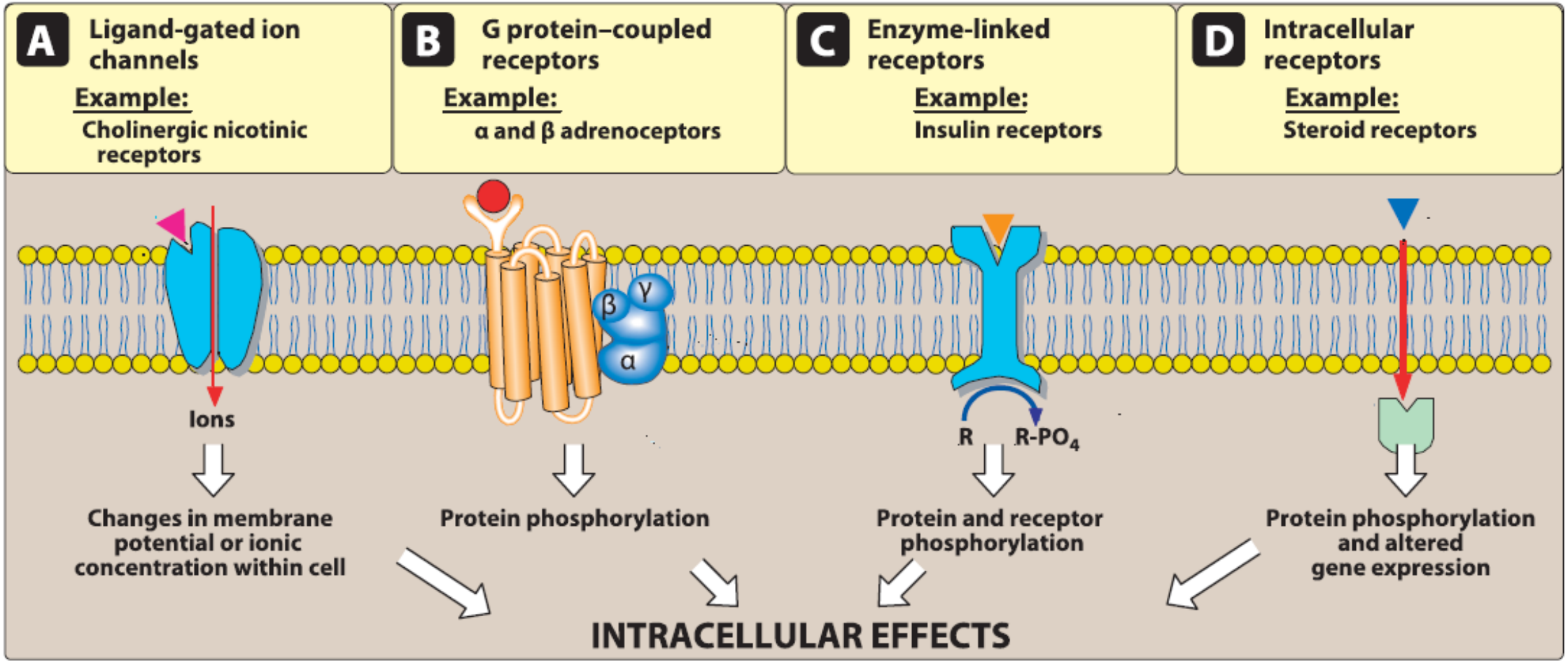
Receptors exist in at least two states, inactive (R) and active (R*), that are in reversible equilibrium



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.



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 y-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.

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.

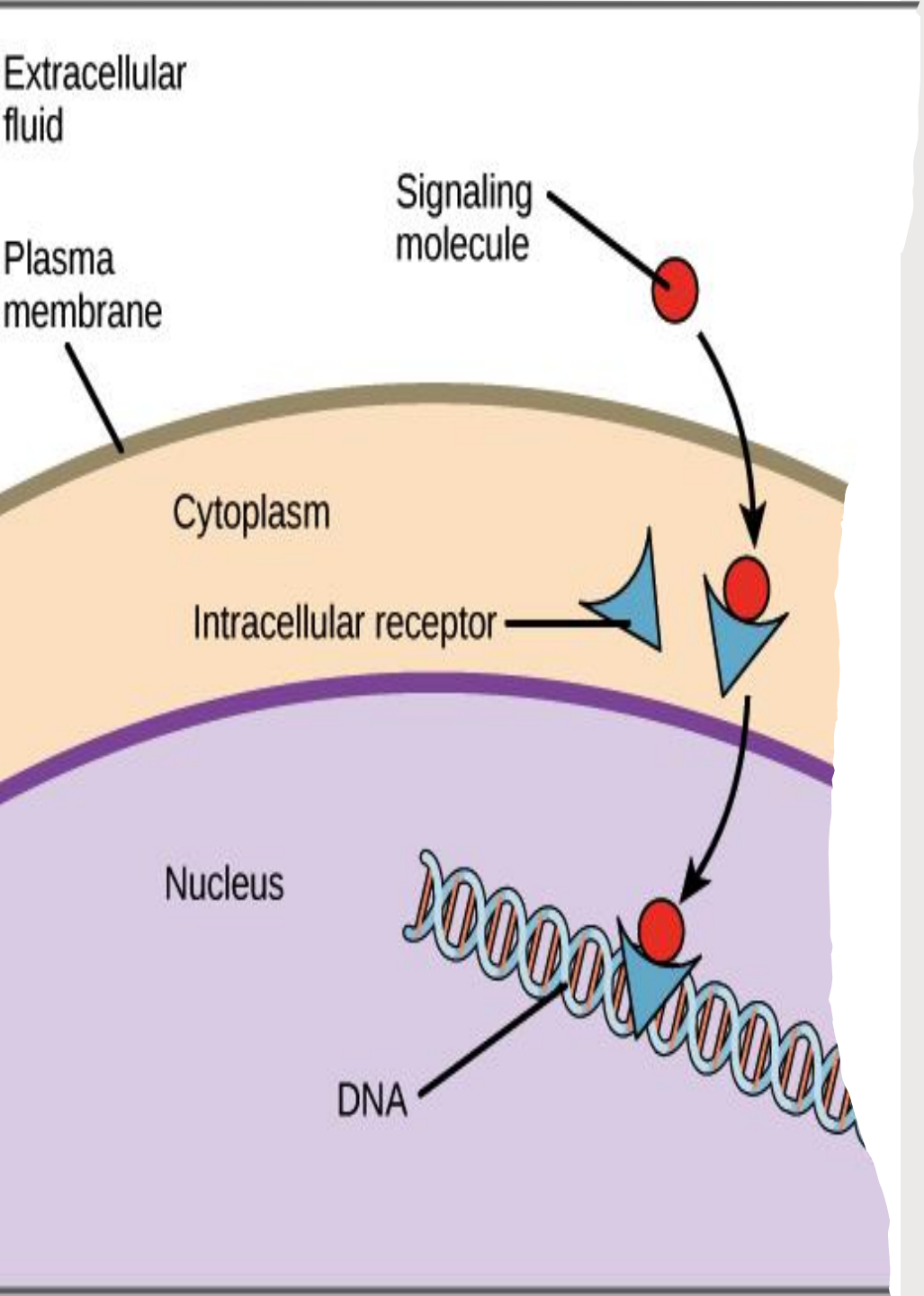
second messengers

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



- 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.

D. Characteristics of signal transduction

Signal transduction has two important features:

1) The ability to amplify small signals.

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

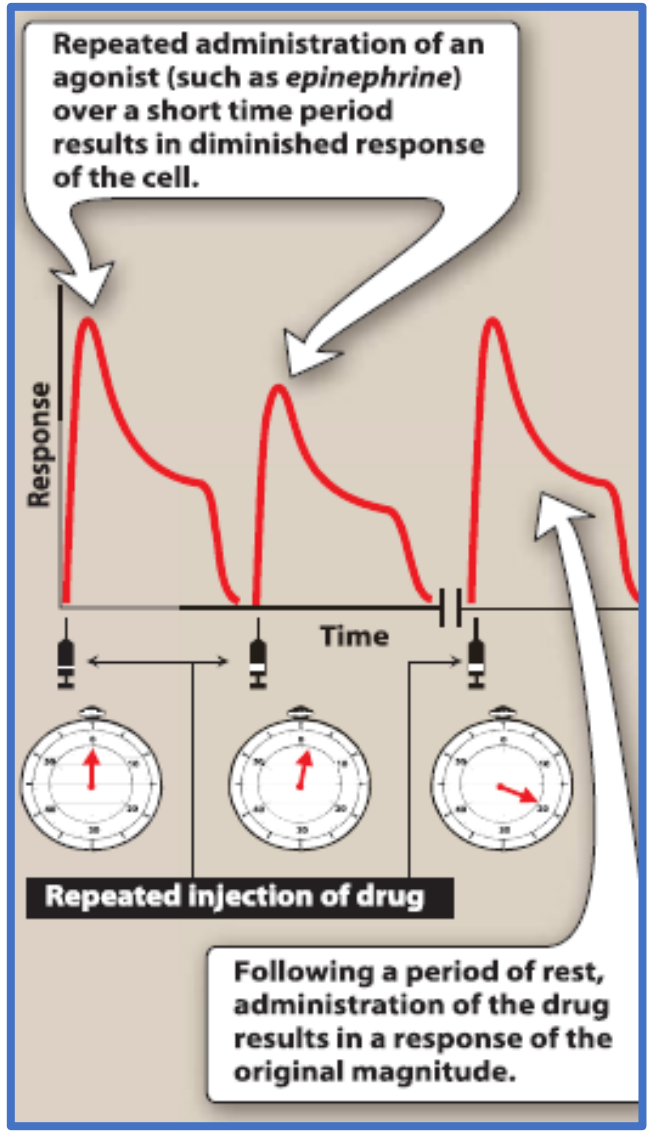
About 99% of insulin receptors are "spare" providing an immense functional reserve that ensures that adequate mounts of glucose enter the cell.

And 5% to 1 0% of the total β-adrenoceptors 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.

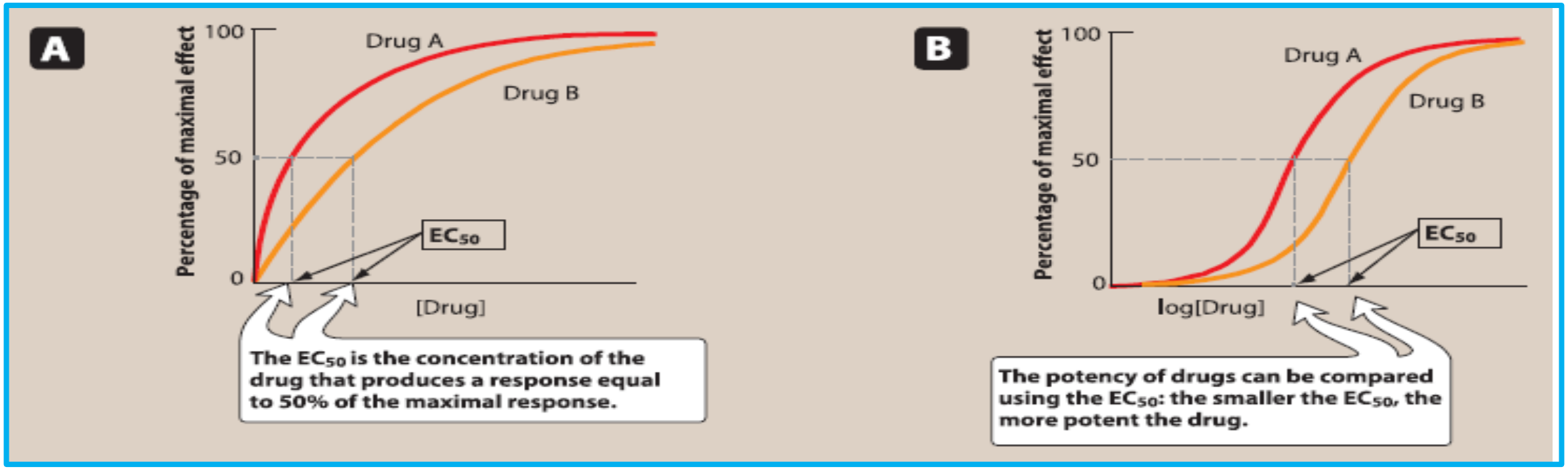


DOSE-RESPONSE RELATIONSHIPS

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).

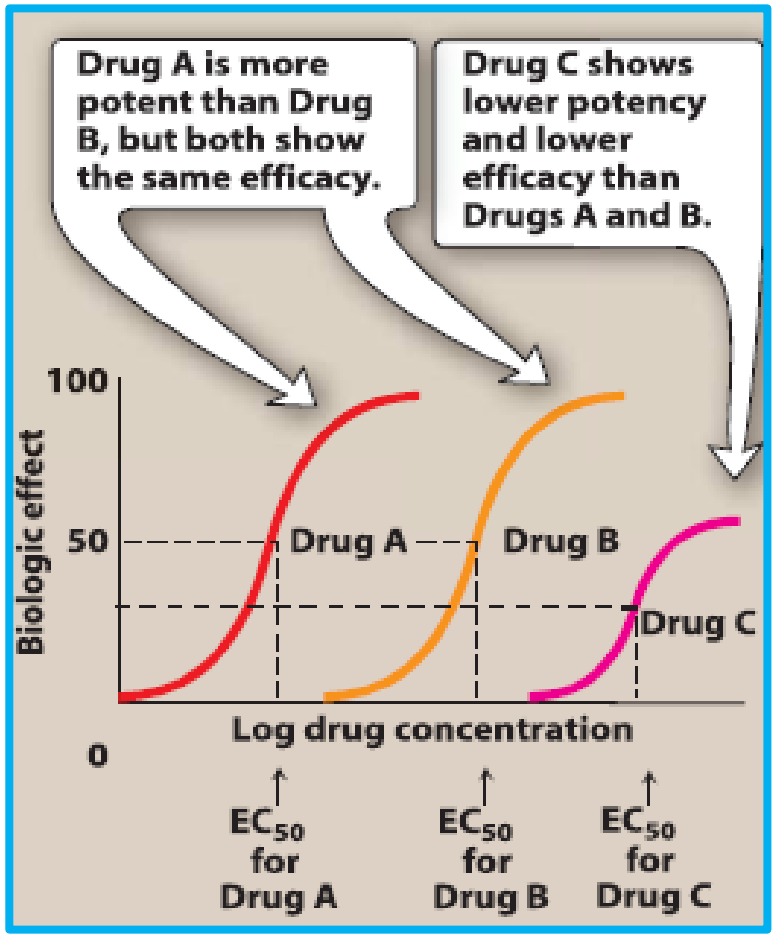
1. Potency: Potency is a measure of the amount of drug necessary to produce an effect. The concentration of drug producing 50% of the maximum effect (EC_{50}) is often used to determine potency.



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.

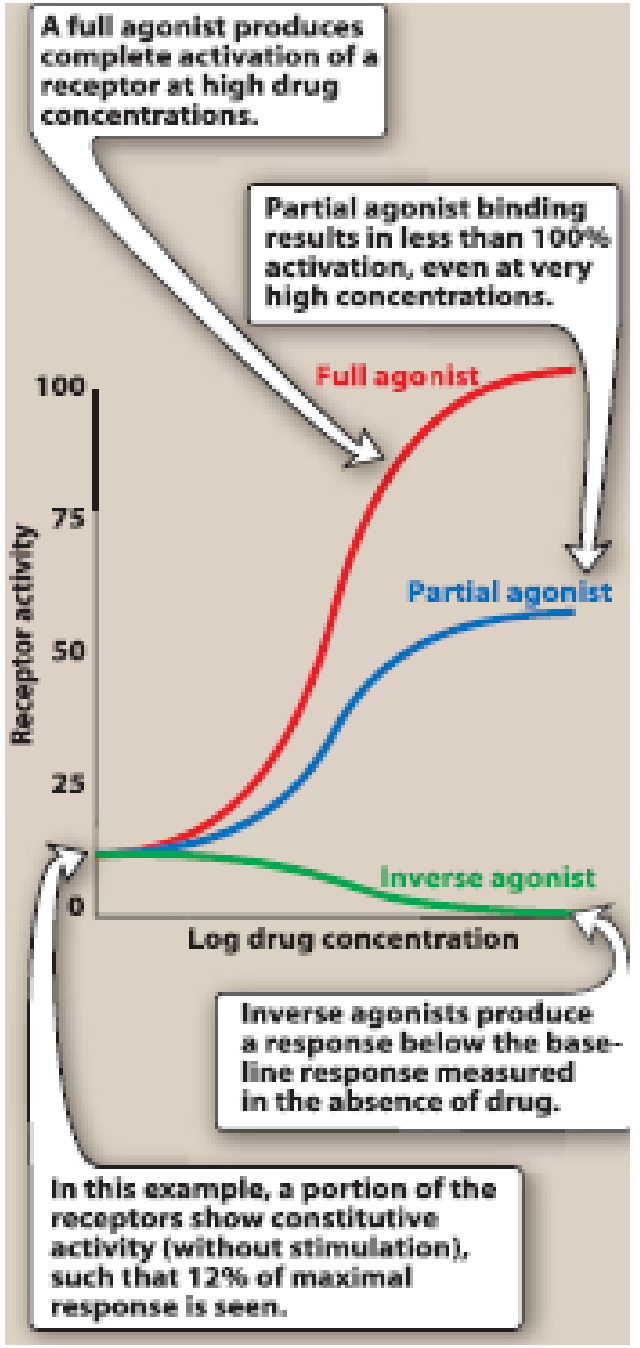
Efficacy is a more clinically useful characteristic than potency, since a drug with greater efficacy is more therapeutically beneficial than one that is more potent.



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 Emax· For example, phenylephrine is a full agonist at α_1-adrenoceptors, because it produces the same Emax as the endogenous ligand, norepinephrine.



Partial agonists

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.

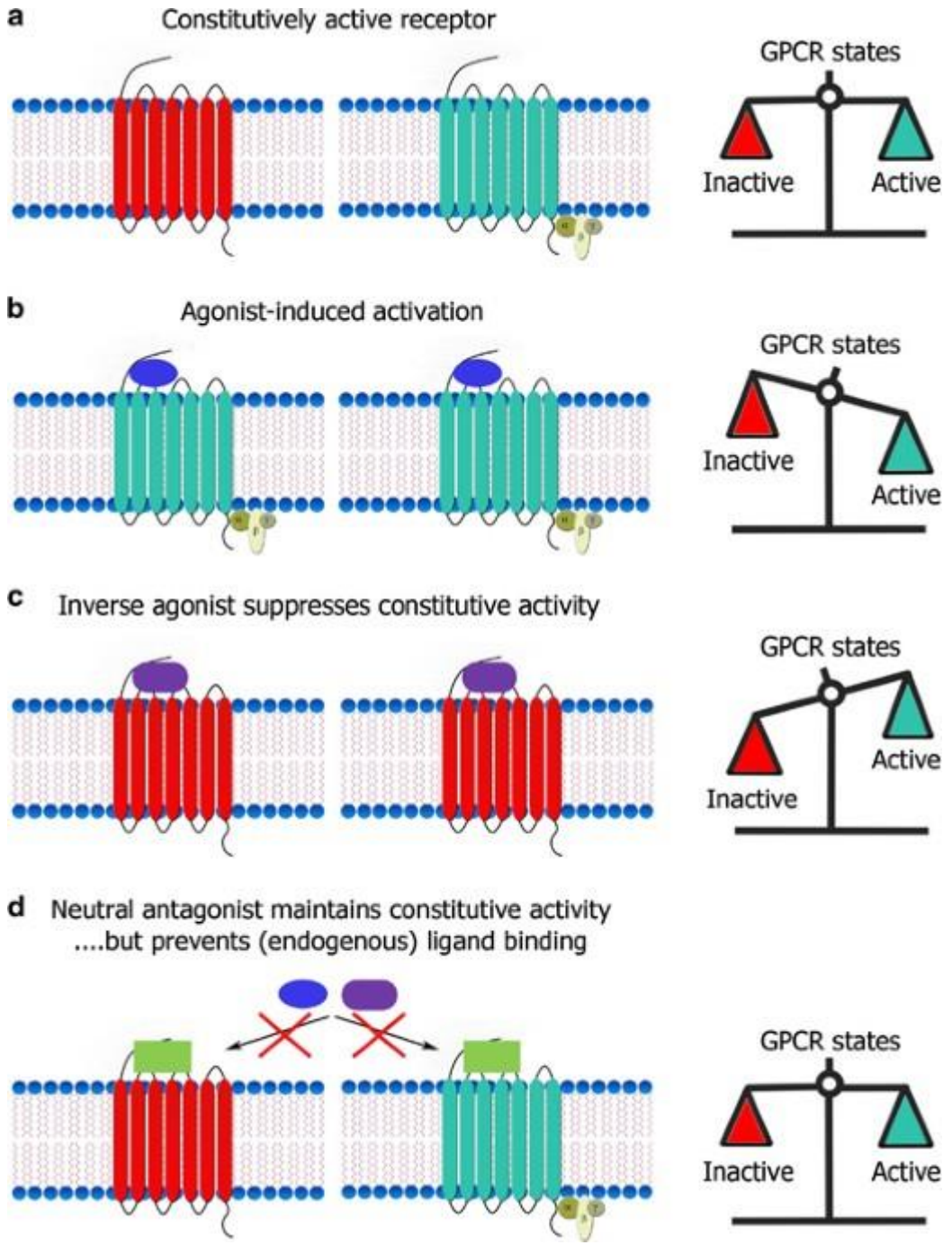
This potential of partial agonists to act as both an agonist and antagonist may have therapeutic utility.

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.



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.

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.

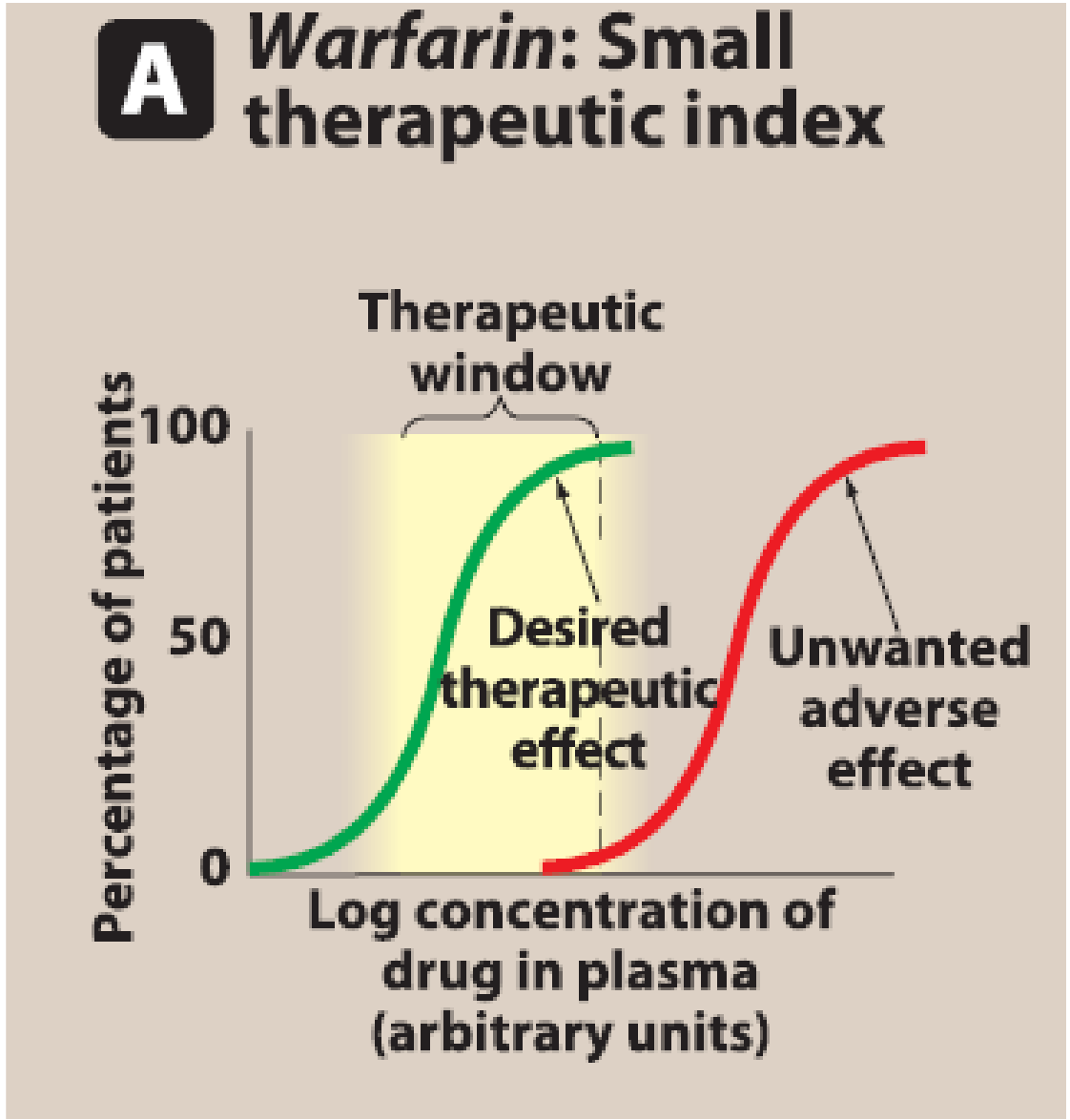
Epinephrine is an agonist at β_2-adrenoceptors on bronchial smooth muscle, which causes the muscles to relax. This functional antagonism is also known as "physiologic antagonism."

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.

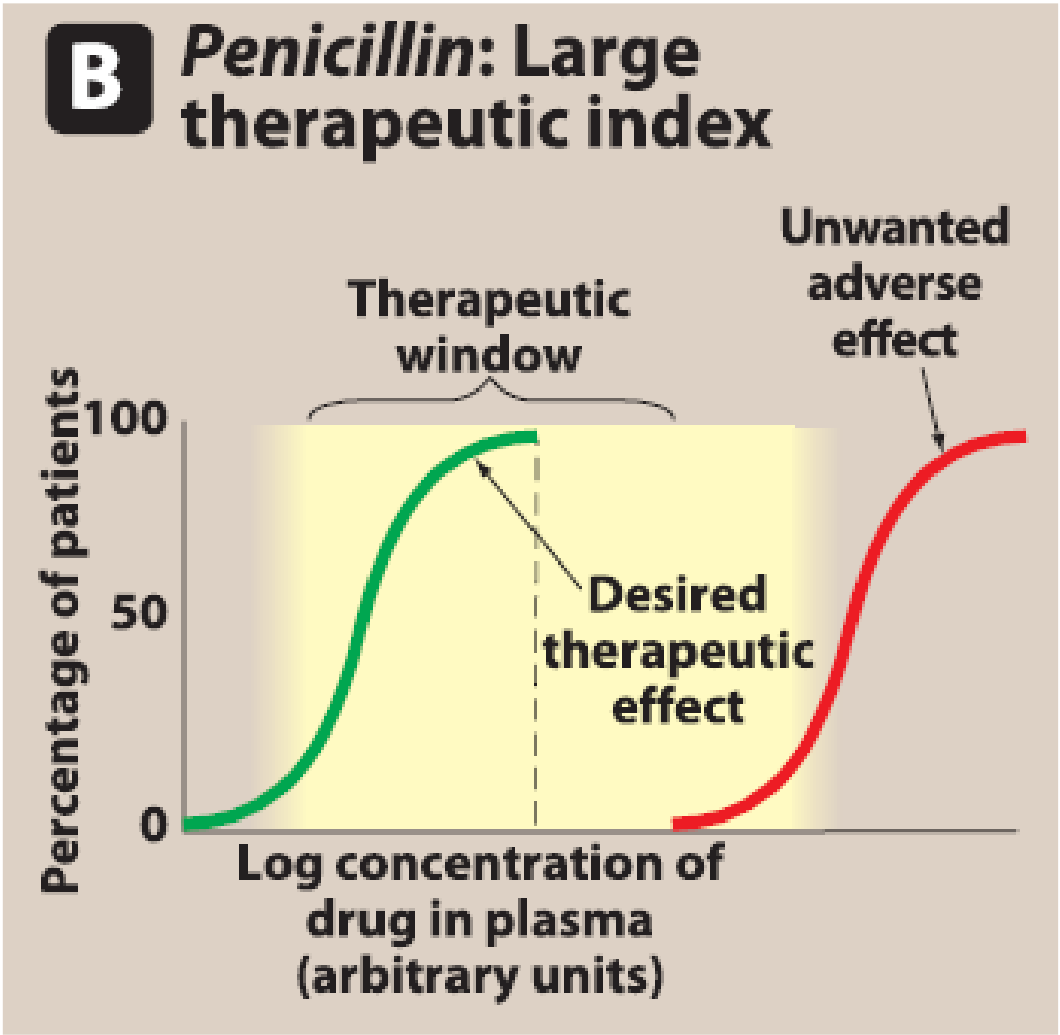


- B. Clinical usefulness of the therapeutic Index

- The TI 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.



References

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

Thank you