Drug–Receptor Interactions and Pharmacodynamics

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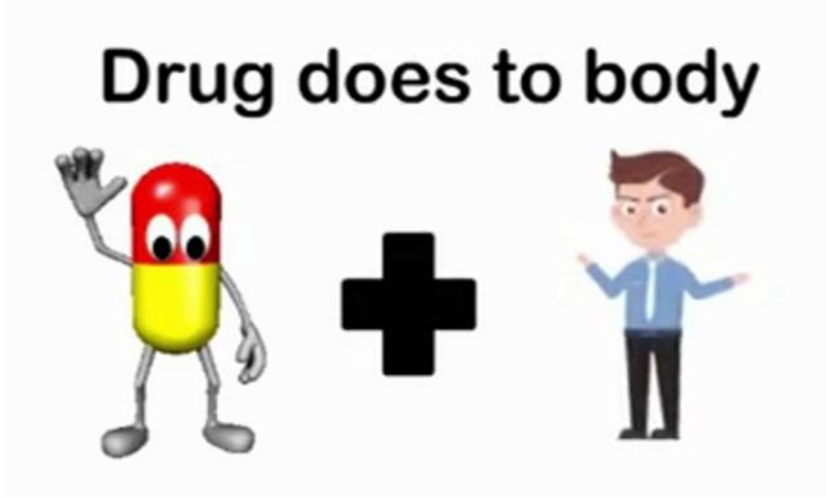


Pharmacodynamics describes the actions of a drug on the body and the influence of drug concentrations on the magnitude of the response.

Most drugs exert their effects, both beneficial and harmful, by interacting with receptors (that is, specialized target macromolecules) present on the cell surface or within the cell.

The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by aprocess called 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 series of reactions that ultimately result in a specific intracellular response.

"Second messenger"

or effector molecules are part of the cascade of events that translates agonist binding into a cellular response.

A. The drug-receptor complex

Cells have many different types of receptors, each of which is specific for a particular agonist and produces a unique response.

for example ,Cardiac cell membranes,, contain p-adrenergic receptors that bind and respond to epinephrine or norepinephrine. Cardiac cells also contain muscarinic receptors that bind and respond to acetylcholine.

These two receptor populations dynamically interact to control the heart's vital functions.
The magnitude of the cellular response is proportional to the number of drug receptor complexes.

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.

B. Receptor states

Receptors exist in at least two states, inactive (R) and active (R*),

Binding of agonists causes the equilibrium to shift from R to R* to produce a biologic effect.

Antagonists are drugs that bind to the receptor but do not increase the fraction of R*, instead stabilizing the fraction of R.

Some drugs (partial agonists) shift the equilibrium from R to R*, but the fraction of R* is less than that caused by an agonist.

The magnitude of biological effect is directly related to the fraction of R*.

In summary, agonists, antagonists, and partial agonists are examples of molecules or ligands that bind to the activation site on the receptor and can affect the fraction of R*.

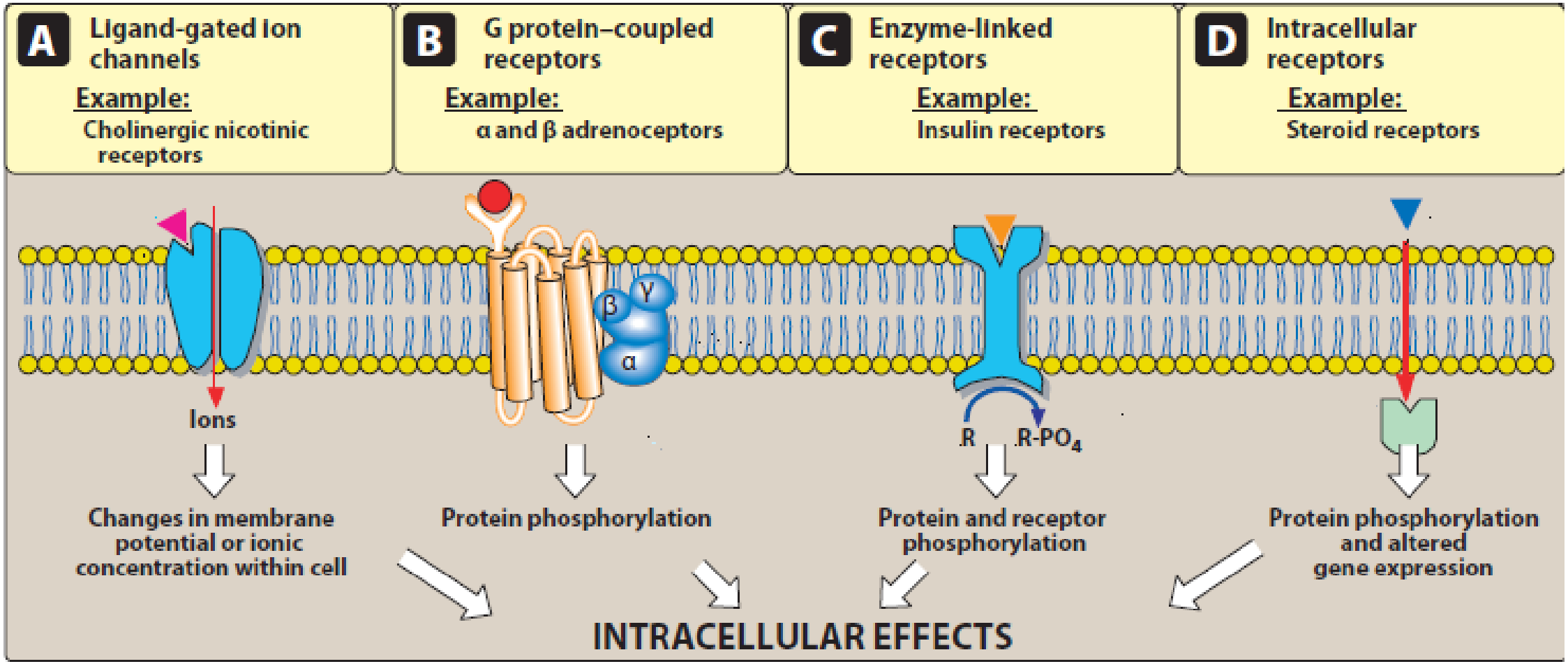
C. Major receptor families

A receptor is defined as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can act as receptors for drugs or endogenous agonists.

These receptors may be divided into four families:

1) ligand-gated ion channels
2) G protein-coupled receptors
3) enzyme-linked receptors.
4) intracellular receptors.

hydrophilic ligands interact with receptors that are found on the cell surface. In contrast, hydrophobic ligands enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells.



Transmembrane signaling mechanisms.

1. Transmembrane ligand-gated ion channels:

The extracellular portion of ligand-gated ion channels usually contains the ligand binding site. This site regulates the shape of the pore through which ions can flow across cell membranes.

The channel is usually closed until the receptor is activated by an agonist, which opens the channel briefly for a few milliseconds.

these receptors mediate diverse functions, including neurotransmission, and cardiac or muscle contraction.

For example,
stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium outflux, generating an action potential in a neuron or contraction in skeletal muscle.

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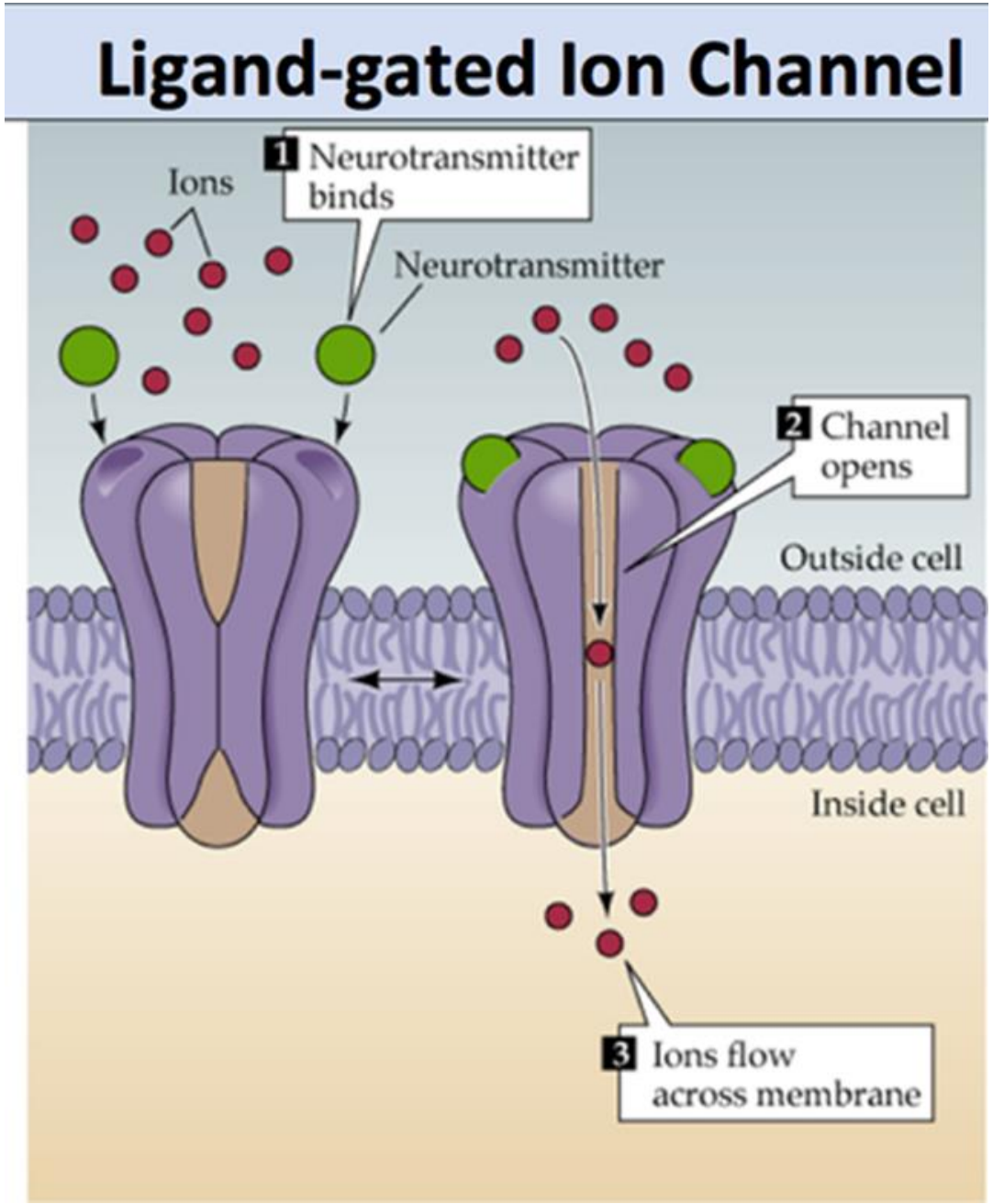
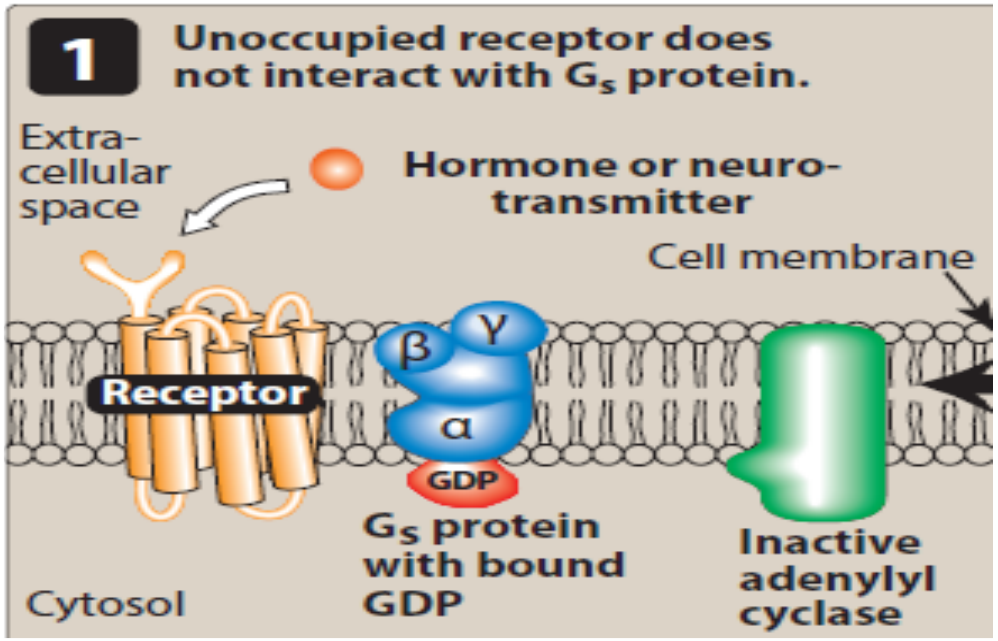
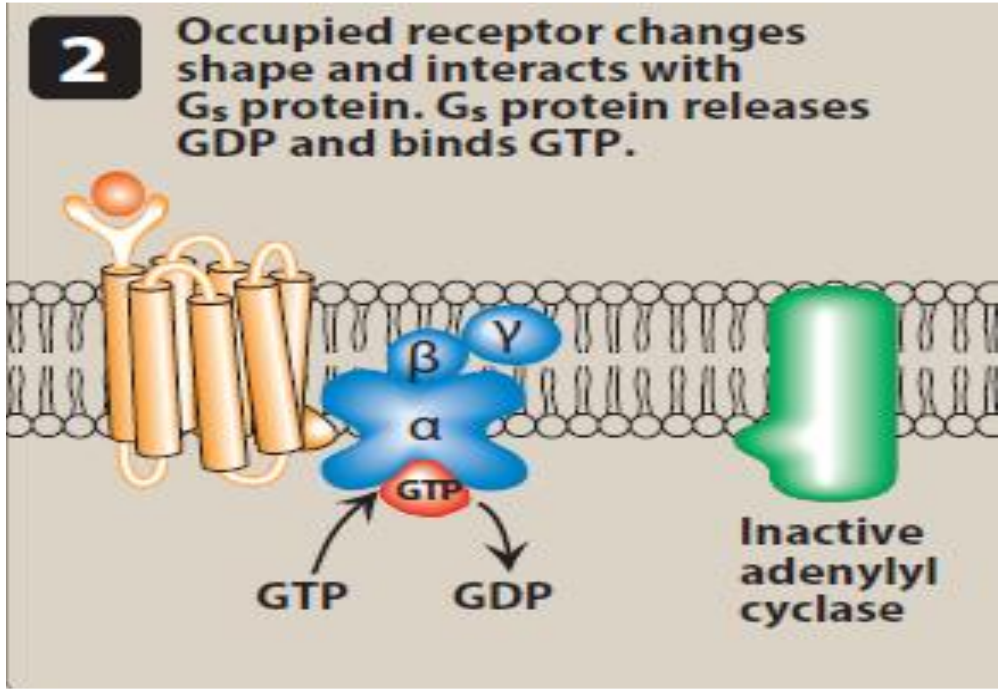
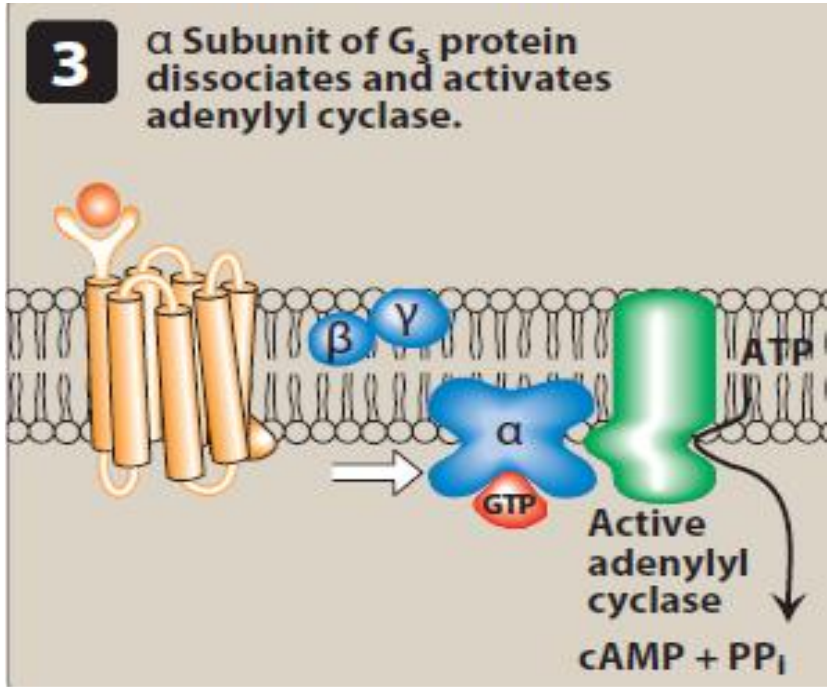
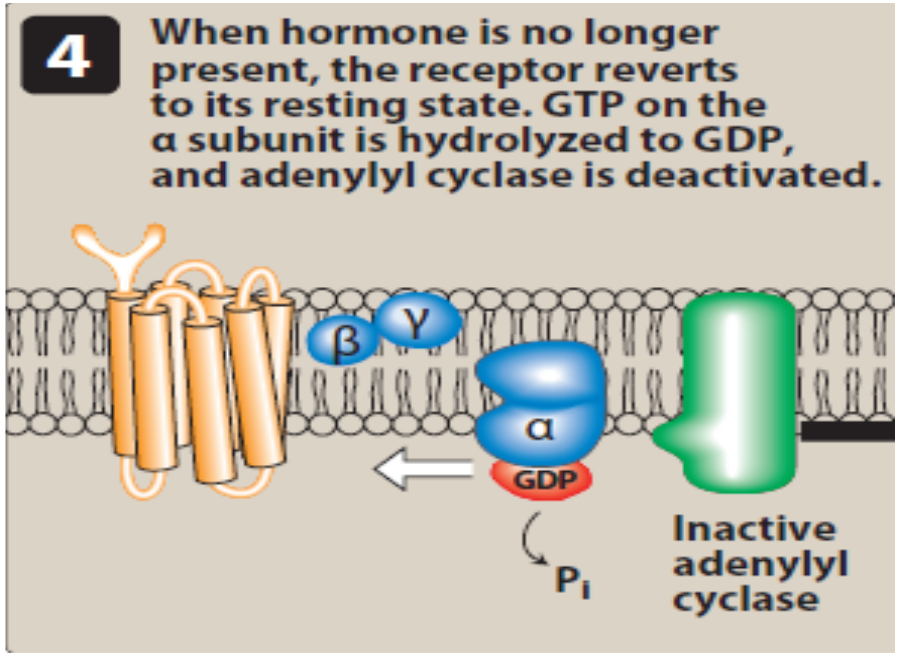
Ligand-gated Ion Channel











The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase

2. **Transmembrane G protein–coupled receptors:**

The extracellular domain of this receptor contains the ligand-binding area, and the intracellular domain interacts (when activated) with a G protein or effector molecule.

There are many kinds of G proteins (for example, Gs, Gi, and Gq), but they all are composed of three protein subunits.

The α subunit binds guanosine triphosphate (GTP), Binding of an agonist to the receptor increases GTP binding to the α subunit, causing dissociation of the α-GTP complex from the βγ complex.

. These responses usually last several seconds to minutes.

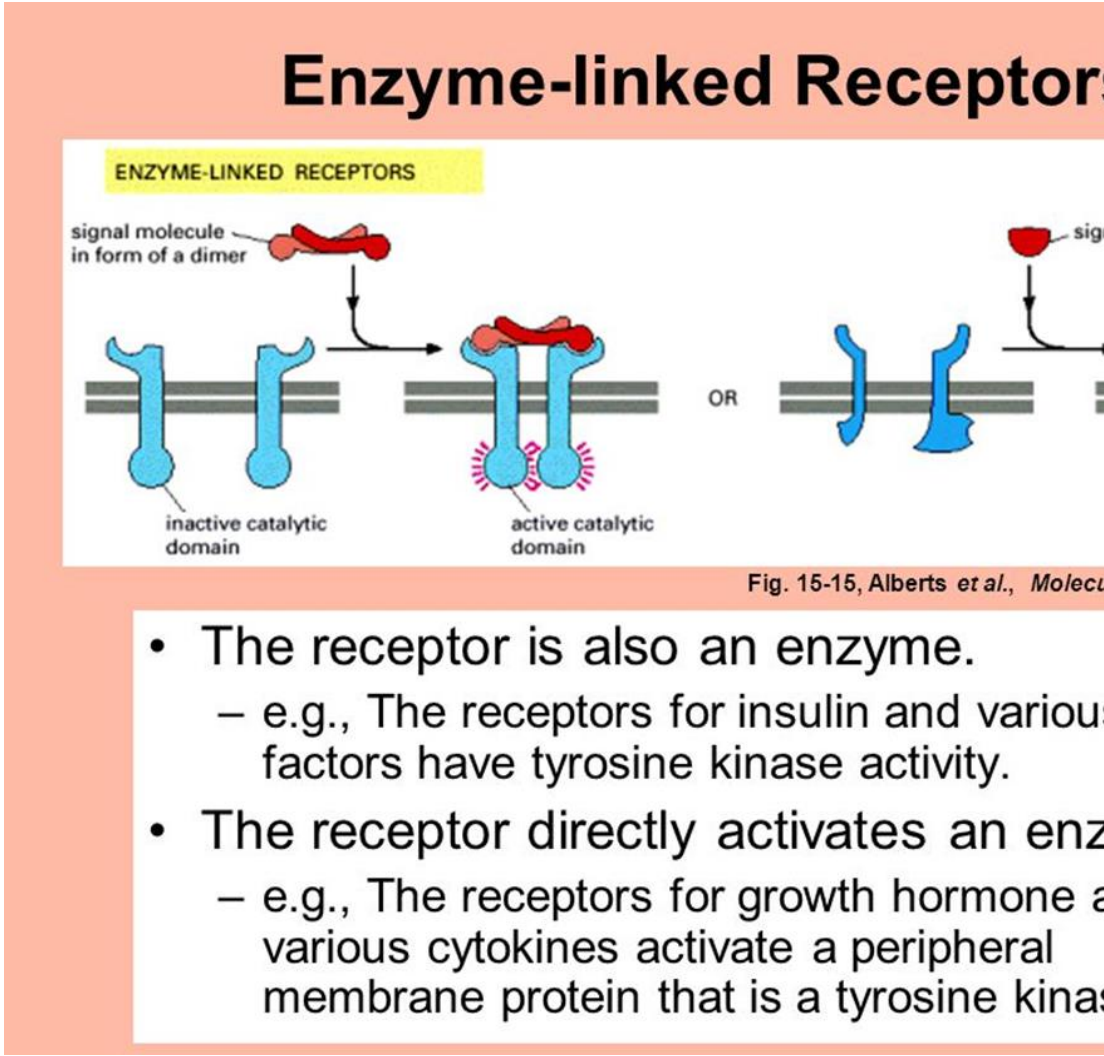
3. Enzyme-linked receptors:

This family of receptors consists of a protein that may form
dimers or multi subunit complexes.

When activated, these
receptors undergo conformational changes resulting in increased cytosolic enzyme activity, depending on their structure and function (

This response lasts on the
order of minutes to hours.

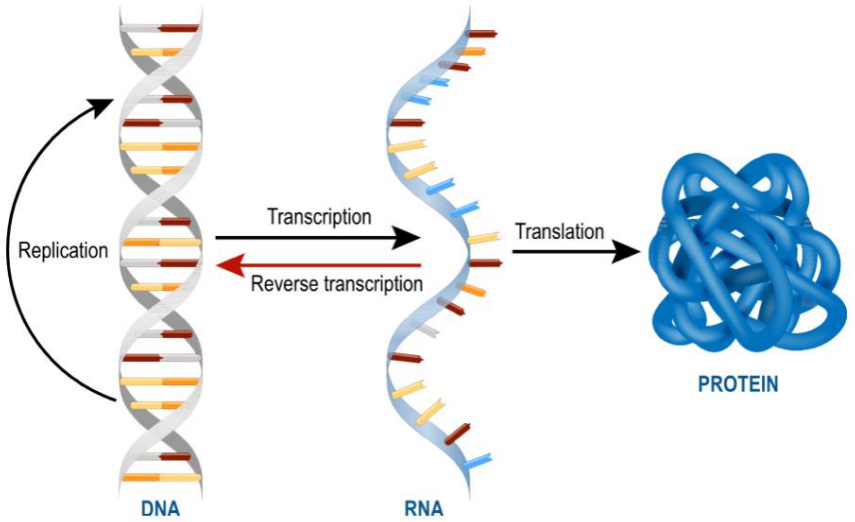
The most common enzyme-linked
receptors **(epidermal growth factor, platelet-derived growth
factor, atrial natriuretic peptide, insulin, and**

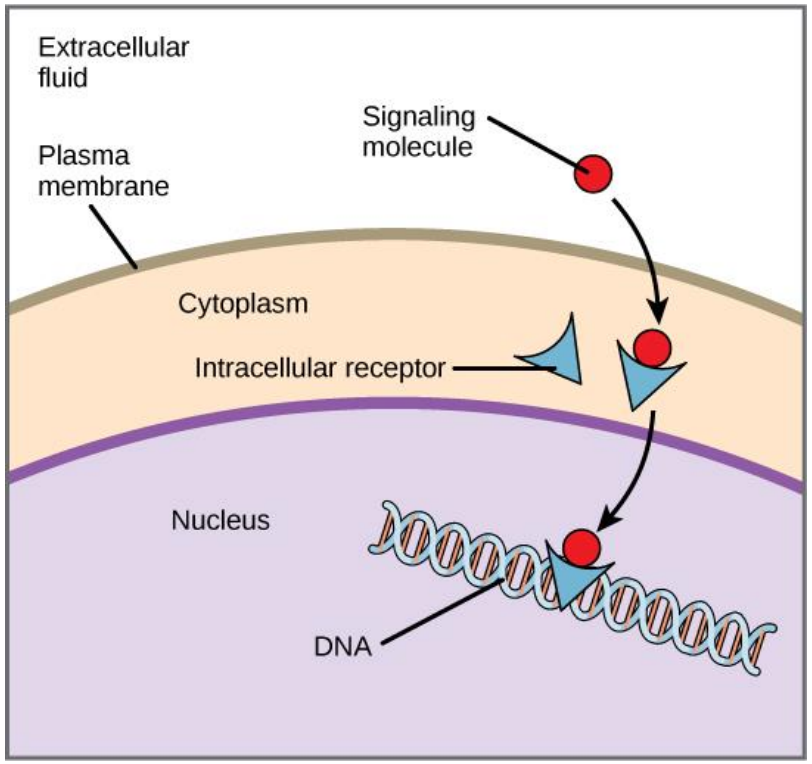


The activated receptor phosphorylates tyrosine residues on itself and then other specific proteins. Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch. For example, when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself. In turn, the phosphorylated receptor phosphorylates other peptides or proteins that subsequently activate other important cellular signals. This cascade of activations results in a multiplication of the initial signal, much like that with G protein–coupled receptors.

4. Intracellular receptors

The fourth family of receptors differs 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 .
The activation or inactivation of transcription factors alters the transcription of DNA into RNA and subsequently translation of RNA into proteins.
The effect of drugs or endogenous ligands that activate intracellular receptors takes hours to days to occur.





The time course of activation and response of these receptors is on the order
of hours to days. For example, steroid hormones exert their action on target cells via
intracellular receptors. Other targets of intracellular ligands are structural proteins,
enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic
agents such as *paclitaxel*, the enzyme dihydrofolate reductase is the target of
antimicrobials such as *trimethoprim*, and the 50S subunit of the bacterial ribosome is
the target of macrolide antibiotics such as *erythromycin*.

D. Characteristics of signal transduction

Signal transduction has two important features: 1) the ability to amplify small signals and 2) mechanisms to protect the cell from excessive stimulation.

1. Signal amplification: A characteristic of G protein-linked and enzyme-linked receptors is the ability to amplify signal intensity and duration via the signal cascade effect. Additionally, activated G proteins persist for a longer duration than does the original agonist-receptor complex. The binding of albuterol, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal

are mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response. 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 amounts of glucose enter the cell.

On the other hand, only about 5% to 10% of the total B3-adrenoceptors in the heart are spare. Therefore, little functional reserve exists in the failing heart, because most receptors must be occupied to obtain maximum contractility

Desensitization and down-regulation of receptors:

Repeated or continuous
administration of an agonist or antagonist often leads to changes in the responsiveness of the receptor. The receptor may become desensitized due to too much agonist stimulation (Figure 2.6), resulting in a diminished response.

This phenomenon, called tachyphylaxis, is often due to phosphorylation that renders receptors unresponsive to the agonist. In addition, receptors may be internalized within the cell, making them unavailable for further agonist interaction (down-regulation).
Some receptors,
particularly ion channels, require a finite time following stimulation before they can be activated again. During this recovery phase, unresponsive receptors are said to be "refractory." 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. Up-regulation of receptors can make cells more sensitive to agonists and/or more resistant to effects of the antagonist.

Dose-Response Relationship:

Agonist drugs mimic the action of the endogenous ligand for the receptor (for example,
isoproterenol mimics norepinephrine on b1 receptors of
the heart).

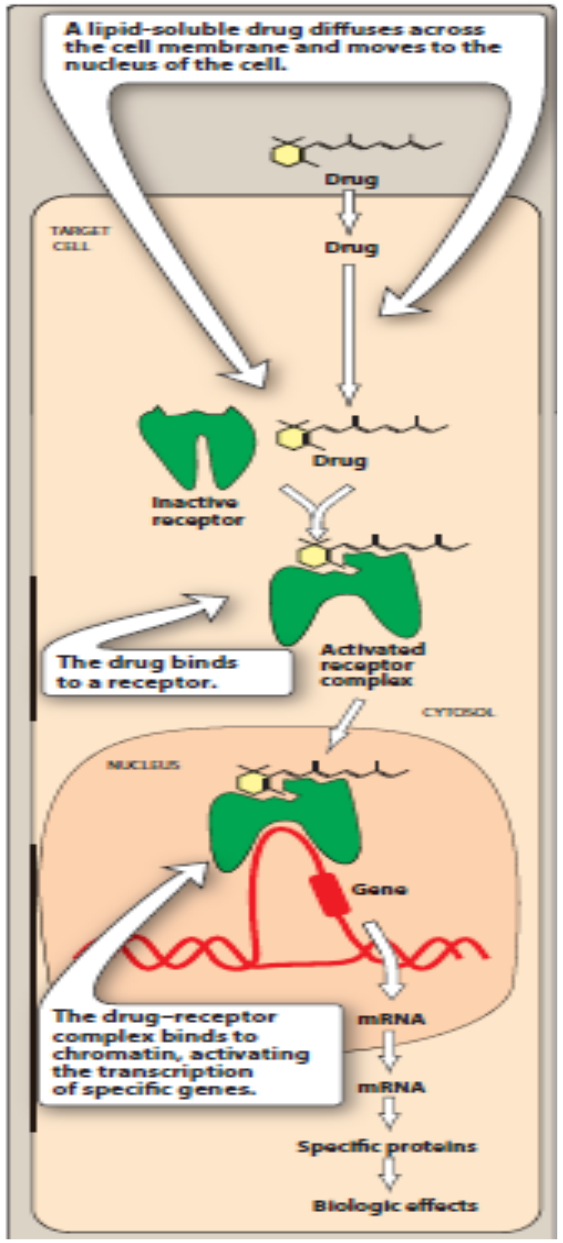
The magnitude of the drug effect depends on receptor sensitivity to the drug and the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug's pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination.

A. Graded dose-response relationship

As the concentration of a drug increases, its pharmacologic effect also gradually increases until all the receptors are occupied (the maximum effect).

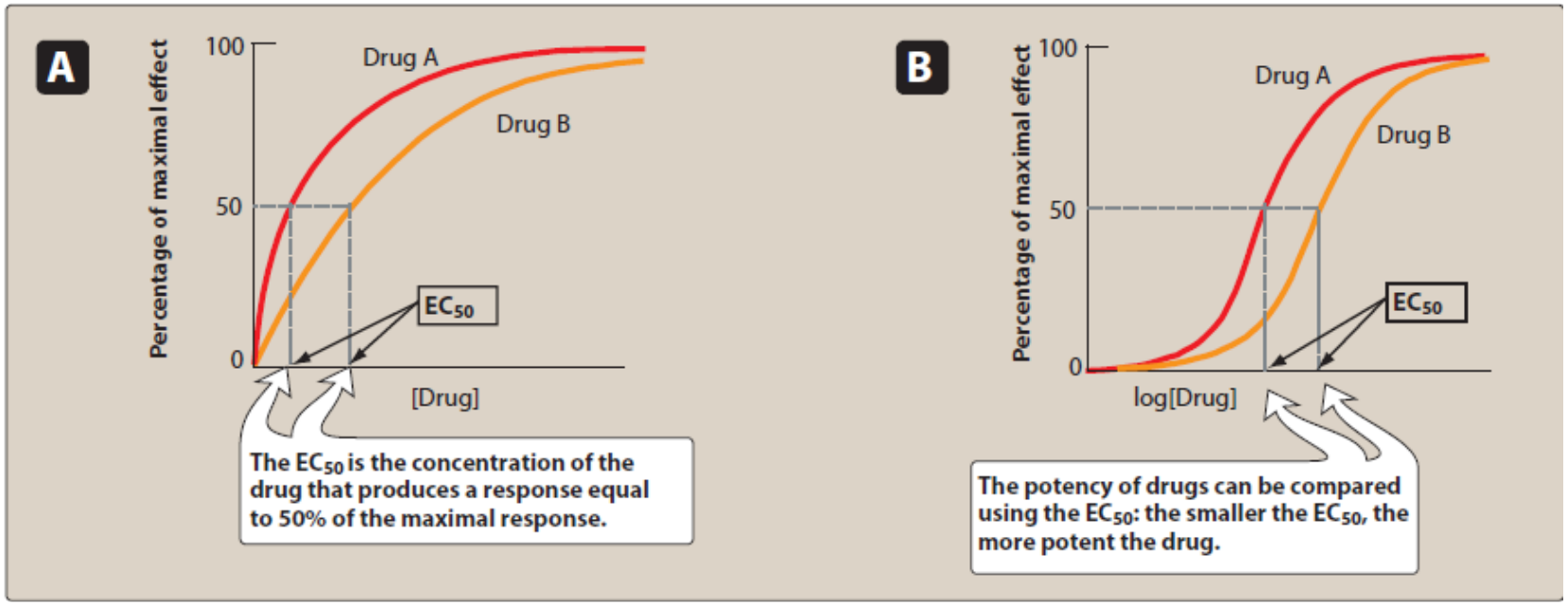
Plotting the magnitude of response against increasing doses of a drug produces a graded dose-response curve.

Two important drug characteristics, potency and efficacy, can be determined by graded dose response curves.



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 (EC50) is often used to determine potency.

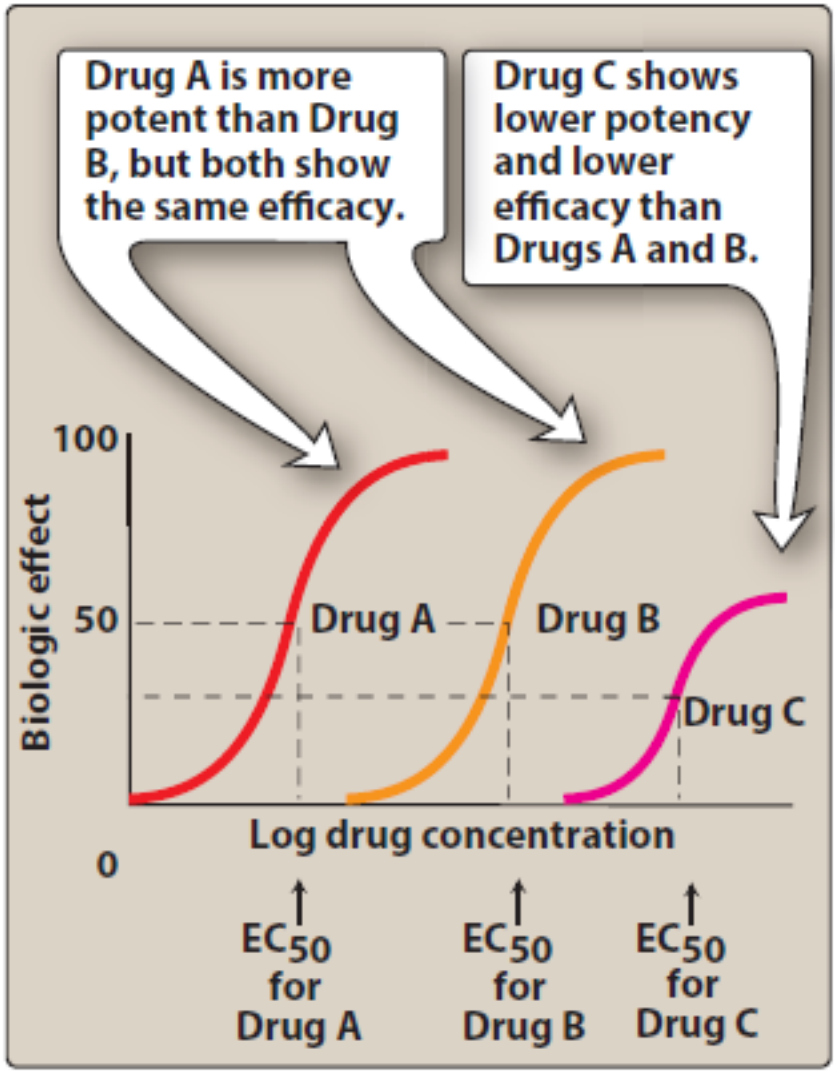
In below figure, The EC50 for Drugs A and B indicate that Drug A is more potent than Drug B, because a lesser amount of Drug A is needed to obtain 50% effect. Therapeutic preparations of drugs reflect their potency. For example, candesartan and irbesartan are angiotensin receptor blockers used to treat hypertension.
The therapeutic dose range for candesartan is 4 to 32 mg, as compared to 75 to 300 mg for irbesartan. Therefore, candesartan is more potent than irbesartan (it has a lower EC50 value). Since the range of drug concentrations that cause from 1% to 99% of maximal response usually spans several orders of magnitude, semilogarithmic plots are used to graph the complete range of doses. the curves become sigmoidal in shape, which simplifies the interpretation of the dose-response curve.



The effect of dose on the magnitude of pharmacologic response. Panel A is a linear graph. Panel B is a semilogarithmic plot of the same data. EC50 = drug dose causing 50% of maximal response.

2. Efficacy: Efficacy is the magnitude of response a drug causes when it interacts with a receptor. Efficacy is dependent on the number of drug receptor complexes formed and the intrinsic activity of the drug (its ability to activate the receptor and cause a cellular response).

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. The maximal response differs between full and partial agonists, even when the drug occupies 100% of the receptors. Similarly, even though an antagonist occupies 100% of the receptor sites, no



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.