Drug Receptor Interactions & Pharmacodynamics

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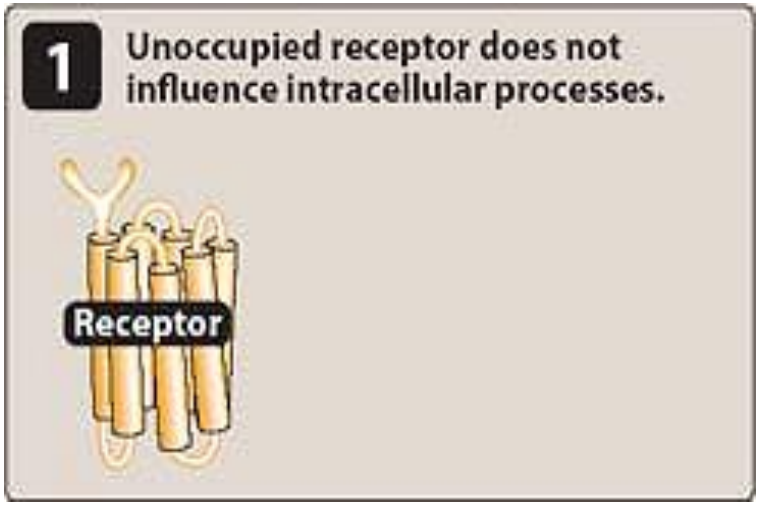
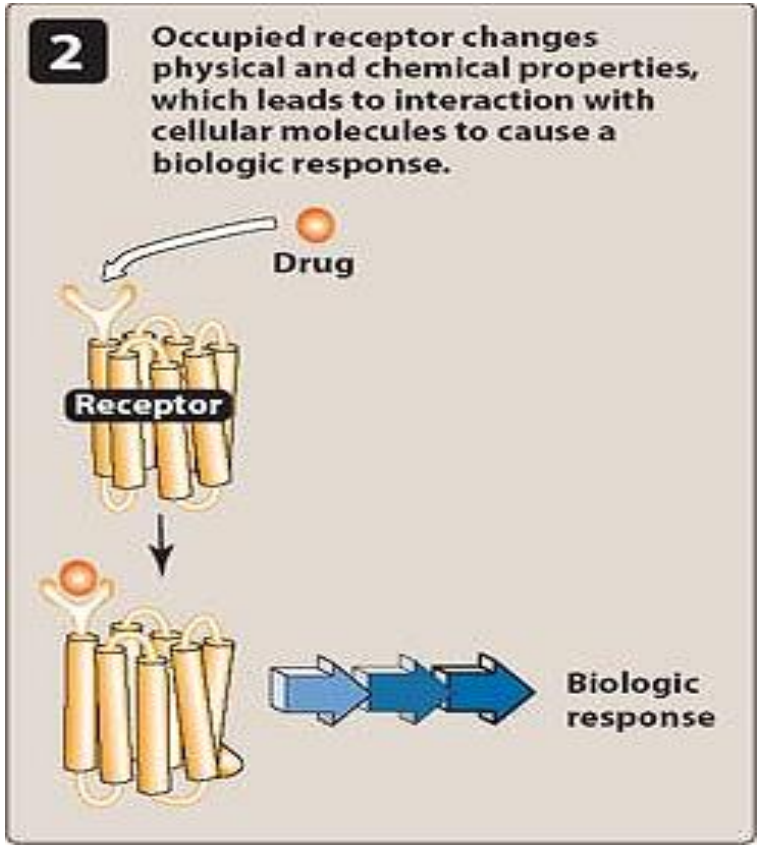
Most drugs exert their effects, both beneficial and harmful, by interacting with receptors that is, specialized target macromolecules present on the cell surface or intracellularly.

Receptors bind drugs and initiate events leading to alterations in biochemical and/or biophysical activity of a cell, and consequently, the function of an organ.

Drugs may bind to enzymes (e.g., inhibition of dihydrofolate reductase by *trimethoprim*), nucleic acids (e.g., blockade of transcription by *dactinomycin*), or membrane receptors (e.g., alteration of membrane permeability by *pilocarpine*).

In each case, the formation of the drug receptor complex leads to a biologic response.





The recognition of a drug by a receptor triggers a biologic response

Most receptors are named to indicate the type of drug/chemical that interacts best with it; e.g., the receptor for histamine is called a histamine receptor.

Cells may also have different types of receptors, each of which is specific for a particular ligand.

On the heart, for example, there are β receptors for norepinephrine, and muscarinic receptors for acetylcholine.

These receptors dynamically interact to control vital functions of the heart.

The magnitude of the response is proportional to the number of drug receptor complexes.

The receptor not only has the ability to recognize a ligand, but can also couple or transduce this binding into a response by causing a conformational change or a biochemical effect.

Not all drugs exert their effects by interacting with a receptor; e.g., *antacids* chemically neutralize excess gastric acid, reducing the symptoms of heartburn.

Chemistry of Receptors and Ligands

Interaction of receptors with ligands involves the formation of chemical bonds.

The successful binding of a drug requires an exact fit of the ligand atoms with the complementary receptor atoms.

The bonds are usually reversible, except for a handful of drugs (e.g., acetylcholinesterase inhibitors) that covalently bond to their targets.

The metaphor of the lock and key is a useful concept for understanding the interaction of receptors with their ligands.

In the presence of a ligand, the receptor undergoes a conformational change to bind the ligand (flexible), which leads to the pharmacologic effect.

Major Receptor Families

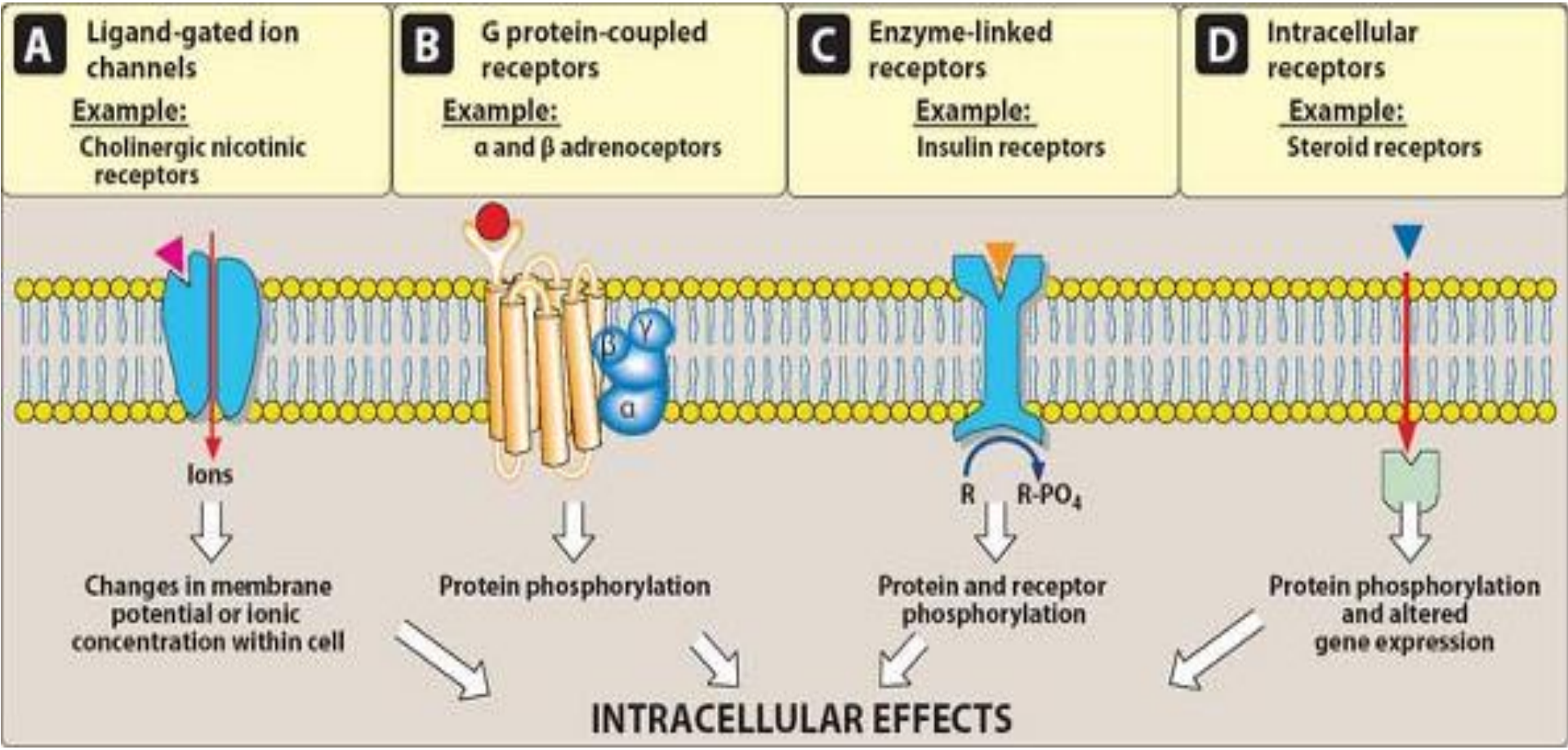
Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response.

Enzymes and structural proteins can be considered to be pharmacologic receptors.

The richest sources of therapeutically pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses.

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.

The type of receptor that a ligand will interact with, depends on the nature of the ligand.



Transmembrane signaling mechanisms.

A. Ligand binds to the extracellular domain of a ligand-gated channel.

B. Ligand binds to a domain of a serpentine receptor, which is coupled to a G protein.

C. Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme.

D. Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor.

A. Ligand-gated ion channels

Responsible for regulation of the flow of ions across cell membranes.

The activity of these channels is regulated by the binding of a ligand to the channel.

Response to these receptors is very rapid, having durations of a few milliseconds.

The nicotinic receptor and the γ-aminobutyric acid (GABA) receptor are important examples of ligand-gated receptors, the functions of which are modified by numerous drugs.

Stimulation of the nicotinic receptor by *acetylcholine* results in sodium influx, activation of contraction in skeletal muscle.

B. G protein coupled receptors

These receptors are linked to a G protein having three subunits, an α subunit that binds guanosine triphosphate (GTP) and a β γ subunit.

Binding of the appropriate ligand to the extracellular region of the receptor activates the G protein so that GTP replaces guanosine diphosphate (GDP) on the α subunit.

Dissociation of the G protein occurs, and both the α-GTP subunit and the β γ subunit subsequently interact with other cellular effectors, usually an enzyme or ion channel.

These effectors then change the concentrations of second messengers that are responsible for further actions within the cell.

Stimulation of these receptors results in responses that last several seconds to minutes.

Second messengers: These are essential in conducting and amplifying signals coming from G protein coupled receptors.

A common pathway turned on by this type of receptors, is the activation of adenylyl cyclase by α-GTP subunits, which results in the production of cyclic adenosine monophosphate (cAMP) a second messenger that regulates protein phosphorylation.

G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers, namely inositol-1,4,5-trisphosphate and diacylglycerol.

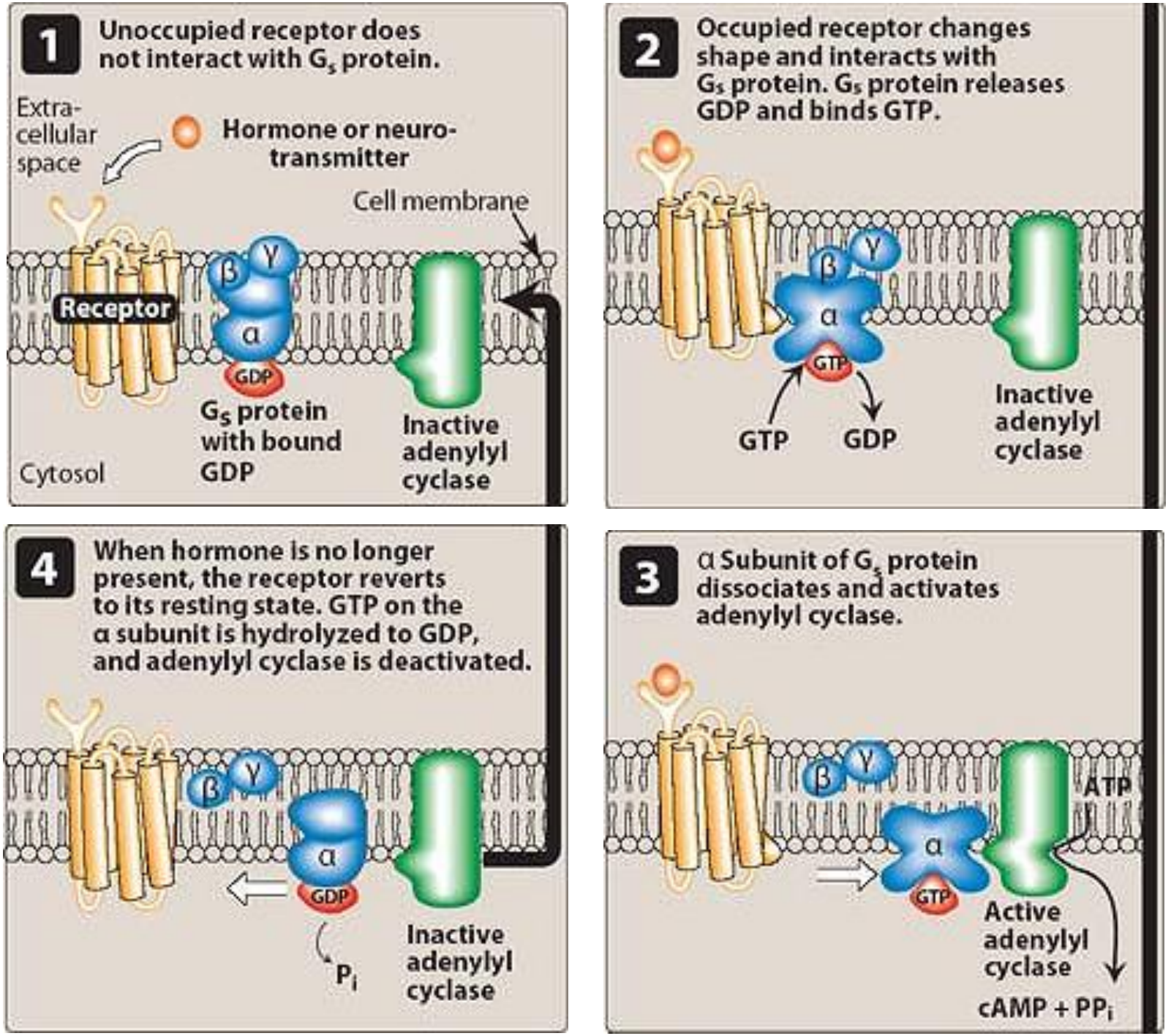
These effectors are responsible for the regulation of intracellular free calcium concentrations, and of other proteins as well.

This family of receptors transduces signals derived from odors, light, and numerous neurotransmitters, including norepinephrine, dopamine, serotonin, and acetylcholine.

G protein coupled receptors also activate guanylyl cyclase, which converts (GTP) to cyclic guanosine monophosphate (cGMP).

cGMP signaling is important in only a few cells, e.g., intestinal mucosa and vascular smooth muscle, where it causes relaxation of vascular smooth muscle cells.

Some drugs such as *sildenafil* produce vasodilation by interfering with specific phosphodiesterases, the enzymes that metabolically break down cGMP.


1
Unoccupied receptor does not interact with G_s protein.
Extra-cellular space
Hormone or neuro-transmitter
Cell membrane
Receptor
β
γ
α
GDP
G_s protein with bound GDP
Inactive adenylyl cyclase
Cytosol
2
Occupied receptor changes shape and interacts with G_s protein. G_s protein releases GDP and binds GTP.
β
γ
α
GTP
GTP
GDP
Inactive adenylyl cyclase
3
α Subunit of G_s protein dissociates and activates adenylyl cyclase.
β
γ
α
GTP
ATP
Active adenylyl cyclase
cAMP + PP_i
4
When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated.
β
γ
α
GDP
P_i
Inactive adenylyl cyclase

C. Enzyme-linked receptors

Binding of a ligand to an extracellular domain activates or inhibits the cytosolic enzyme activity.

Duration of responses to stimulation of these receptors is on the order of minutes to hours.

The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, insulin) are those that have a tyrosine kinase activity as part of their structure.

Upon binding of the ligand to receptor subunits, the receptor undergoes conformational changes, converting from its inactive form to an active kinase form.

The activated receptor autophosphorylates, and phosphorylates tyrosine residues on specific proteins.

The addition of a phosphate group can substantially modify the three-dimensional structure of the target protein, thereby acting as a molecular switch.

For example, when the peptide hormone *insulin* binds to its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself.

In turn, the phosphorylated receptor phosphorylates target molecules insulin-receptor substrate peptides that subsequently activate other important cellular signals.

This cascade of activations results in a multiplication of the initial signal, much like that which occurs with G protein coupled receptors.

D. Intracellular receptors

The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular and, therefore, the ligand must diffuse into the cell to interact with the receptor.

This places constraints on the physical and chemical properties of the ligand in that it must have sufficient lipid solubility to be able to move across the target cell membrane.

Because these receptor ligands are lipid soluble, they are transported in the body attached to plasma proteins, such as albumin.

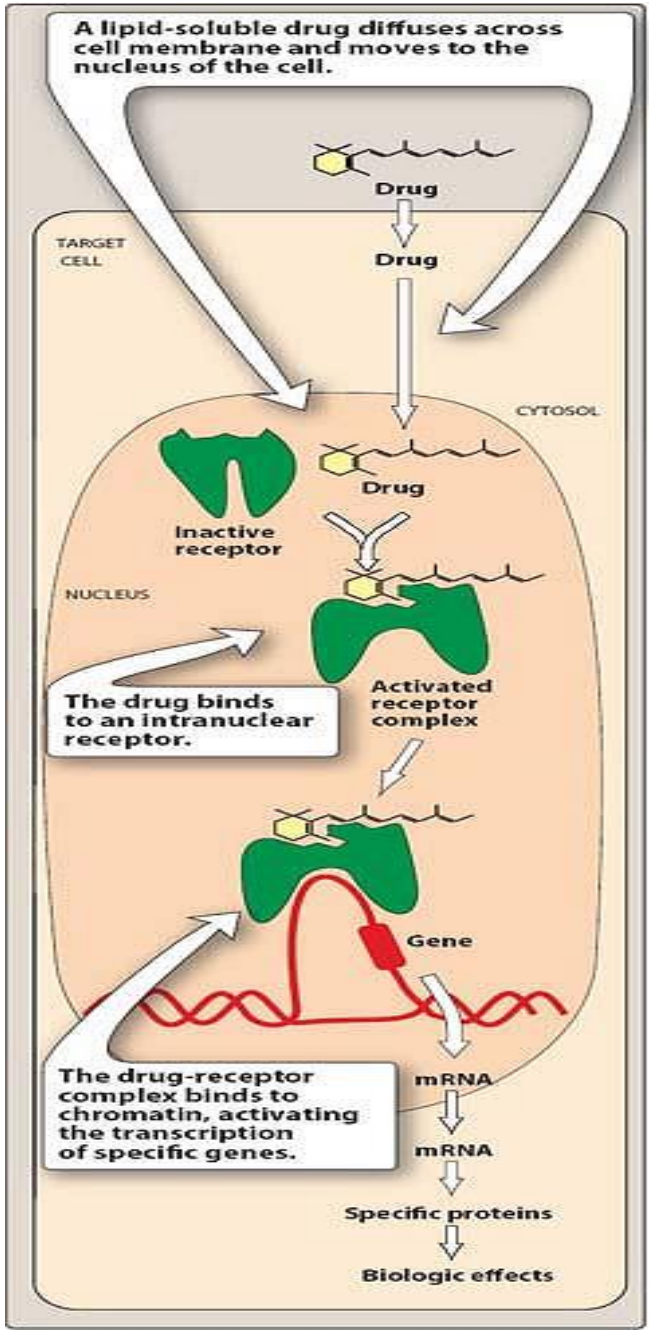
For example, *steroid hormones* exert their action on target cells via this receptor mechanism.

Binding of the ligand with its receptor follows a general pattern in which the receptor becomes activated because of the dissociation of a small repressor peptide.

The activated ligand receptor complex migrates to the nucleus, where it binds to specific DNA sequences, resulting in the regulation of gene expression.

The time course of activation and response of these receptors is much longer than that of the other mechanisms described before.

Because gene expression and, therefore, protein synthesis is modified, cellular responses are not observed until considerable time has elapsed (thirty minutes or more), and the duration of the response (hours to days) is much greater than that of other receptor families.



Mechanism of intracellular receptors

Some Characteristics of Receptors

A characteristic of many receptors, particularly those that respond to hormones, neurotransmitters, and peptides, is their ability to amplify signal duration and intensity.

The family of G protein linked receptors exemplifies many of the possible responses initiated by ligand binding to a receptor.

Specifically, two phenomena account for the amplification of the ligand receptor signal.

First, a single ligand receptor complex can interact with many G proteins, thereby multiplying the original signal many-fold.

Second, the activated G proteins persist for a longer duration than the original ligand receptor complex.

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 from a cell.

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

Spare receptors are exhibited by insulin receptors, where it has been estimated that 99 percent of the receptors are spare.

The human heart, in which about five to ten percent of the total β-adrenoceptors are spare.

An important implication of this observation is that little functional reserve exists in the failing heart; most receptors must be occupied to obtain maximum contractility.

Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor.

When repeated administration of a drug results in a diminished effect, the phenomenon is called tachyphylaxis, and the receptor becomes desensitized to the action of the drug.

The receptors are still present on the cell surface but are unresponsive to the ligand.

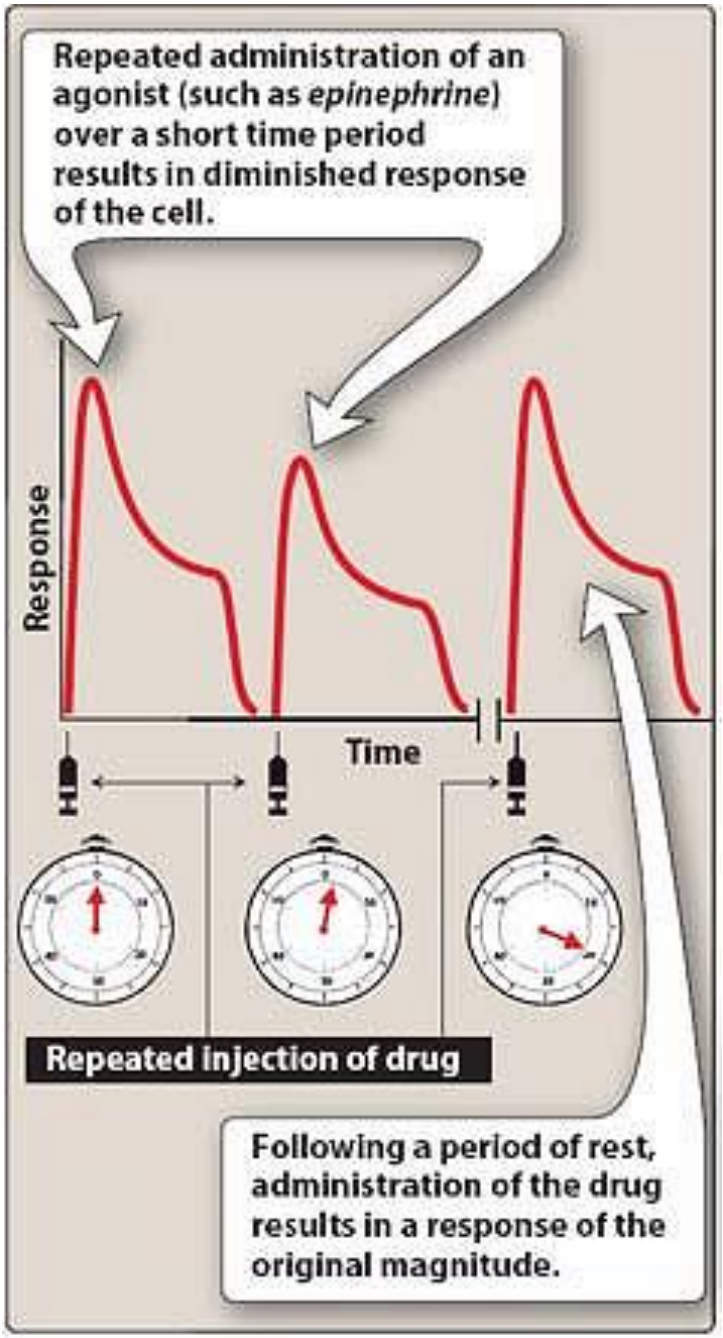
Other types of desensitization occur when receptors are down-regulated.

Binding of the agonist results in molecular changes in the membrane-bound receptors, such that the receptor undergoes endocytosis and is sequestered from further agonist interaction.

These receptors may be recycled to the cell surface, restoring sensitivity, or alternatively, may be further processed and degraded, decreasing the total number of receptors available.

Some receptors require a rest period following stimulation before they can be activated again.

During this recovery phase they are said to be refractory or unresponsive.



Desensitization of receptors

Dose Response Relationships

An agonist is defined as an agent that can bind to a receptor and elicit a biologic response.

The magnitude of the drug effect depends on the drug concentration at the receptor site, which in turn is determined by the dose of drug administered and by factors characteristic of the drug pharmacokinetic profile, such as rate of absorption, distribution, and metabolism.

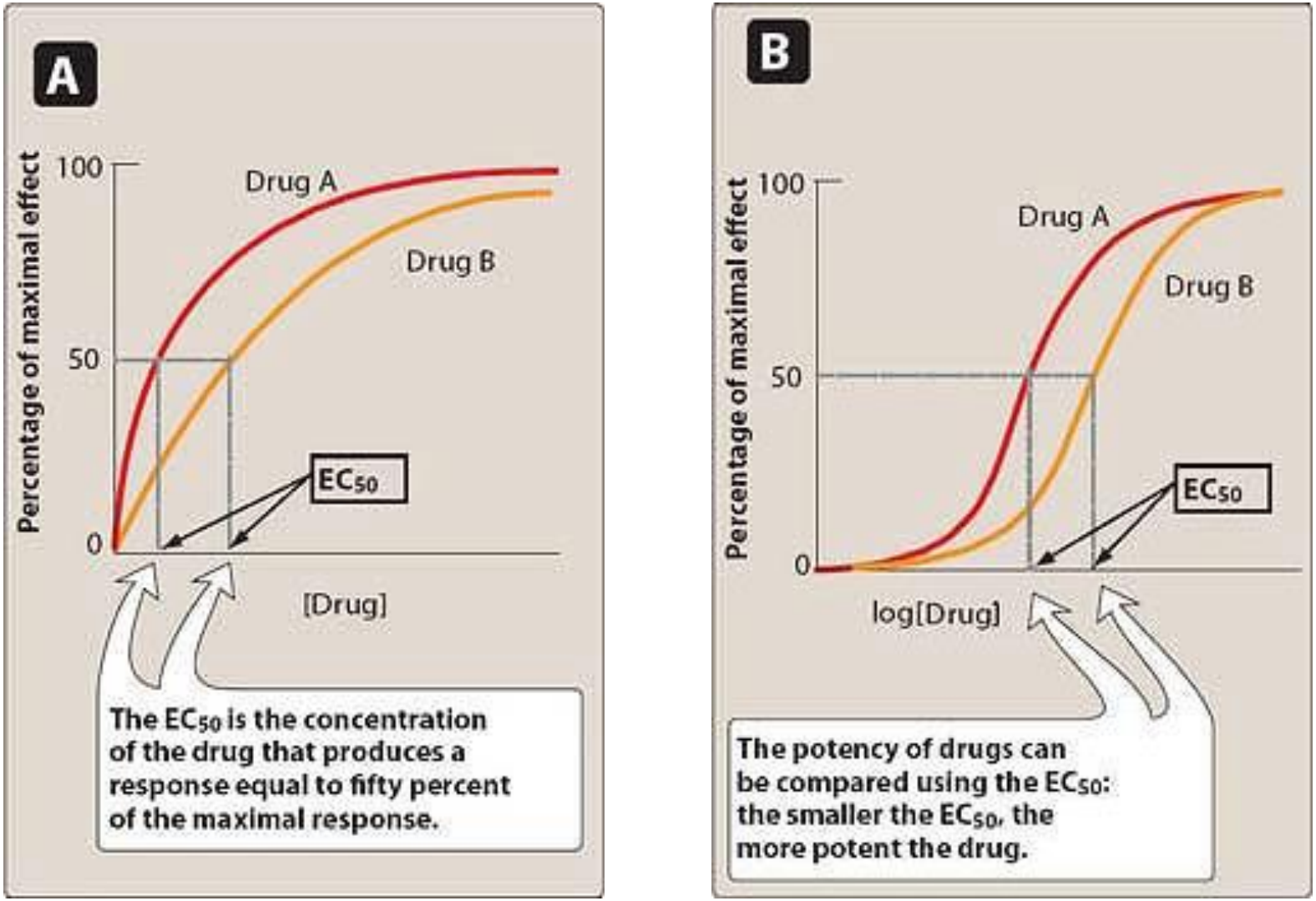
As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases.

The response is a graded effect, meaning that the response is continuous and gradual.

Two important properties of drugs can be determined by graded dose response curves.

The first is Potency: a measure of the amount of drug necessary to produce an effect of a given magnitude.

The concentration producing an effect that is fifty percent of the maximum is used to determine potency; it commonly designated as the EC_{50}.



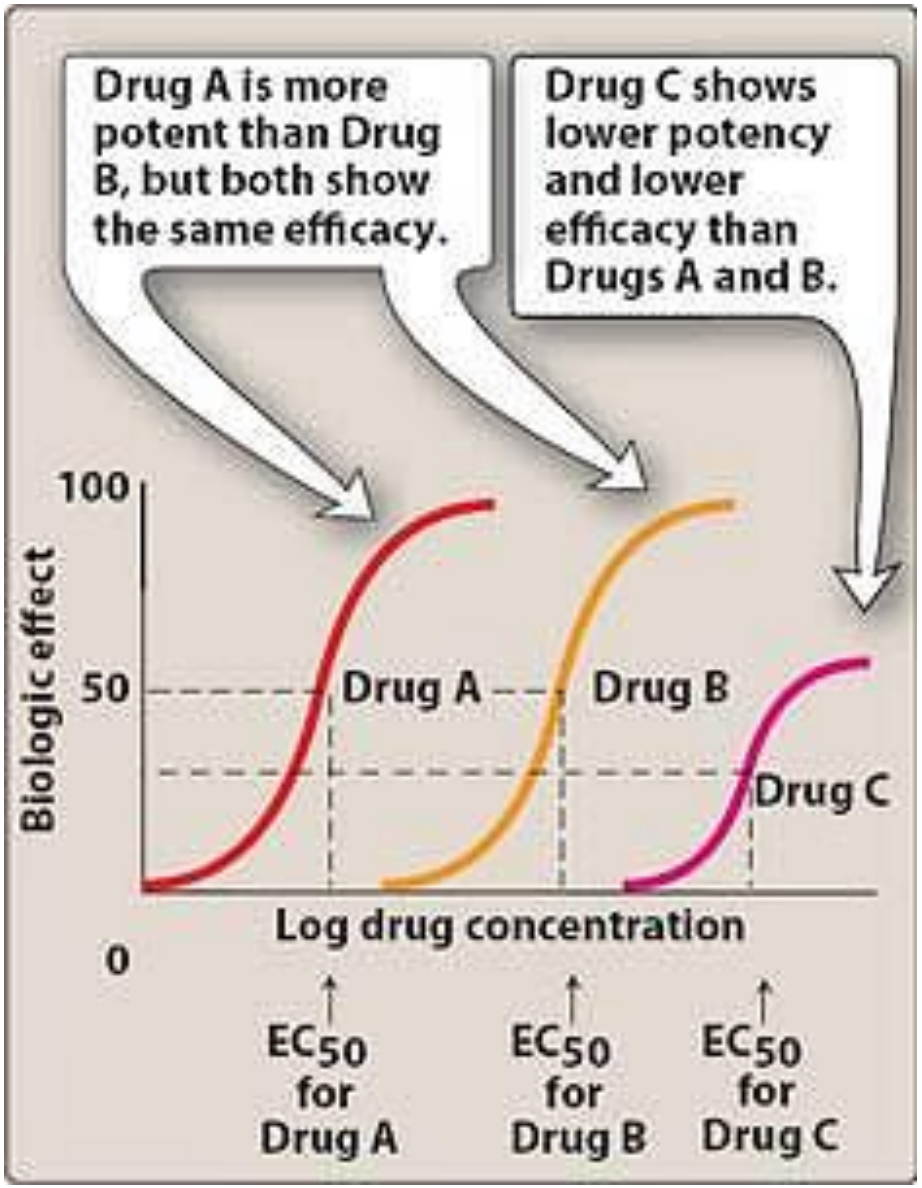
The effect of dose on the magnitude of pharmacologic response.
Panel A is a linear graph.
Panel B is a semilogarithmic plot of the same data.

Efficacy [intrinsic activity]: The second drug property that can be determined from graded dose response plots is the efficacy of the drug.

This is the ability of a drug to illicit a physiologic response when it interacts with a receptor.

Efficacy is dependent on the number of drug receptor complexes formed and the efficiency of the coupling of receptor activation to cellular responses.

A drug with greater efficacy is more therapeutically beneficial than one that is more potent.



Typical dose-response curve for drugs showing differences in potency and efficacy

Agonists: If a drug binds to a receptor and produces a biologic response that mimics the response to the endogenous ligand, it is known as an agonist.

For example, *phenylephrine* is an agonist at α_1-adrenoceptors, because it produces effects that resemble the action of the endogenous ligand, norepinephrine.

Upon binding to α_1-adrenoceptors on the membranes of vascular smooth muscle, *phenylephrine* mobilizes intracellular Ca^{2+}, causing contraction of the actin and myosin filaments.

The shortening of the muscle cells decreases the diameter of the arteriole, causing an increase in resistance to the flow of blood through the vessel, thus, blood pressure therefore rises to maintain the blood flow.

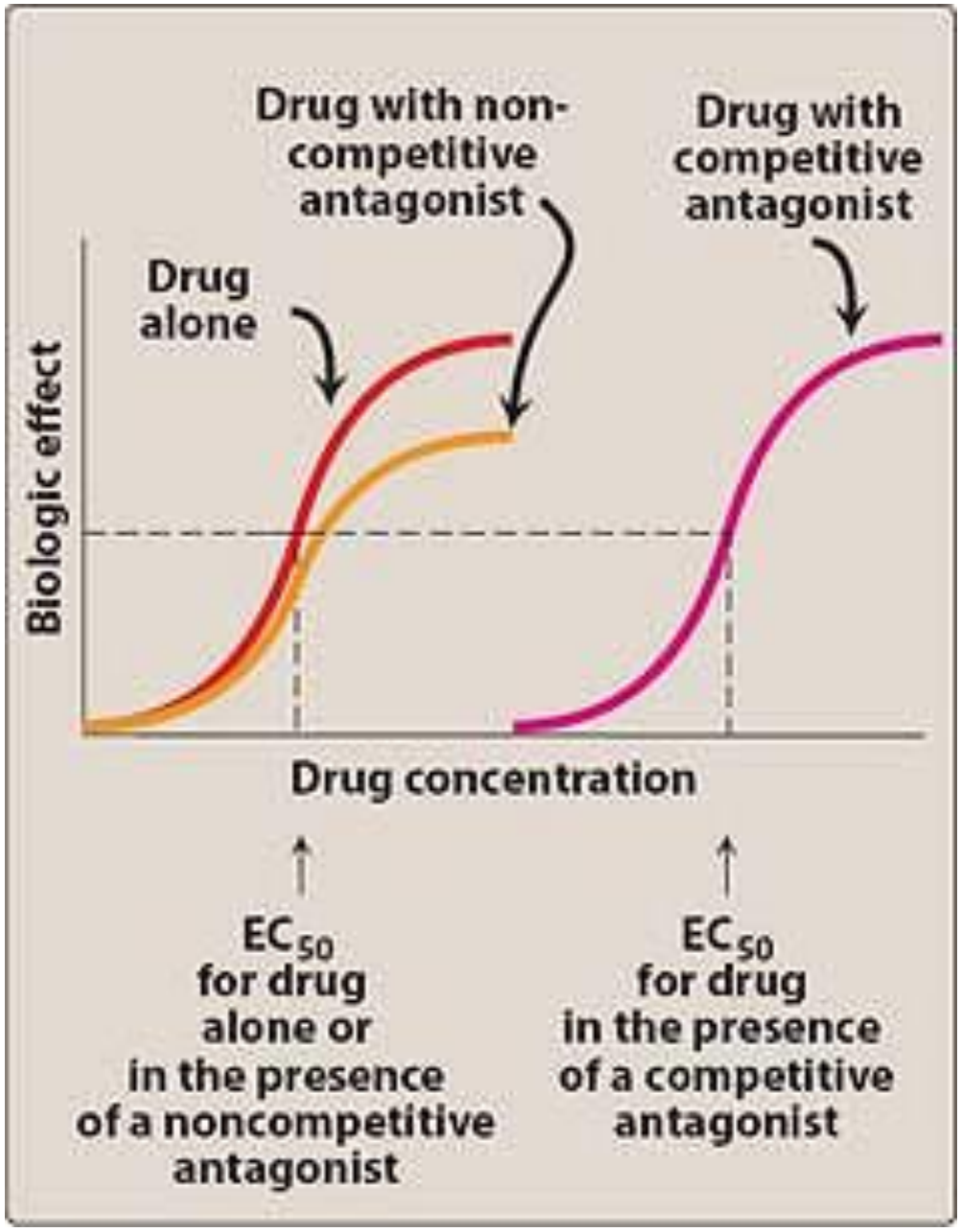
Antagonists: are drugs that decrease the actions of another drug or endogenous ligand.

Many antagonists act on the identical receptor macromolecule as the agonist.

Antagonists, however, have no intrinsic activity and, therefore, produce no effect by themselves.

If both the antagonist and the agonist bind to the same site on the receptor, they are said to be competitive.

For example, the antihypertensive drug *prazosin* competes with the endogenous ligand, norepinephrine, at α_1-adrenoceptors, decreasing vascular smooth muscle tone and reducing blood pressure.



Effects of drug antagonists

A drug may also act as a chemical antagonist by combining with another drug and rendering it inactive.

For example, *protamine* ionically binds to *heparin*, rendering it inactive and antagonizing *heparin's* anticoagulant effect.

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

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

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

Epinephrine is an agonist at β_2-adrenoceptors on bronchial smooth muscle, which causes the muscles to actively relax.

This functional antagonism is also known as physiologic antagonism.

Partial agonists: Partial agonists have efficacies (intrinsic activities) greater than zero, but less than that of a full agonist.

Even if all the receptors are occupied, partial agonists cannot produce an E_{max} of as great a magnitude as that of a full agonist.

A unique feature of these drugs is that, under appropriate conditions, a partial agonist may act as an antagonist of a full agonist.

As the number of receptors occupied by the partial agonist increases, the E_{max} would decrease until it reached the E_{max} of the partial agonist.