Pharmacology I

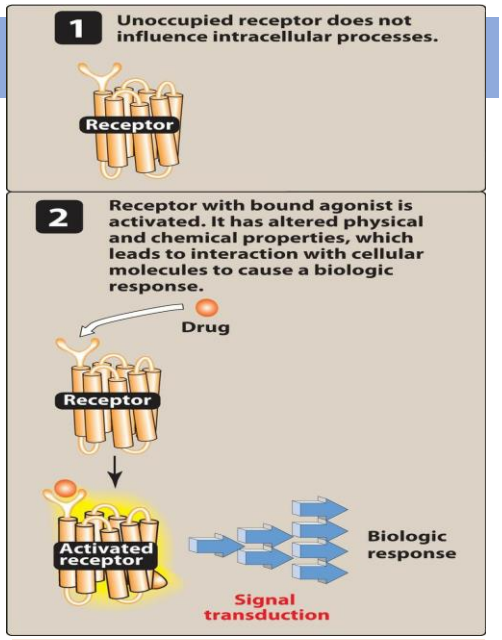
# Drug-Receptor interaction and Pharmacodynamics

**Dr. Marwan Al-Zubeidy**

**Lecture No. : 2**

## Overview

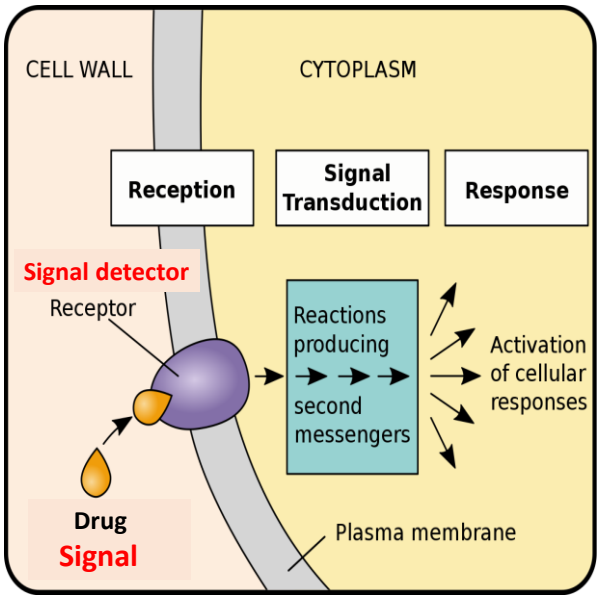
- **Pharmacodynamics** is the actions of a drug on the body.
- Most drugs **exert effects**, both beneficial and harmful, by interacting with **specialized target macromolecules** called **receptors**, which are present on or in the cell.
- **The drug–receptor complex** initiates alterations in biochemical and/or molecular activity of a cell by a process called **signal transduction.**




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

## 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.




## The drug–receptor complex

- Cells have different types of receptors, each of which is specific for a particular agonist and produces a unique response.
- **Cardiac cell membranes**, for example, contain

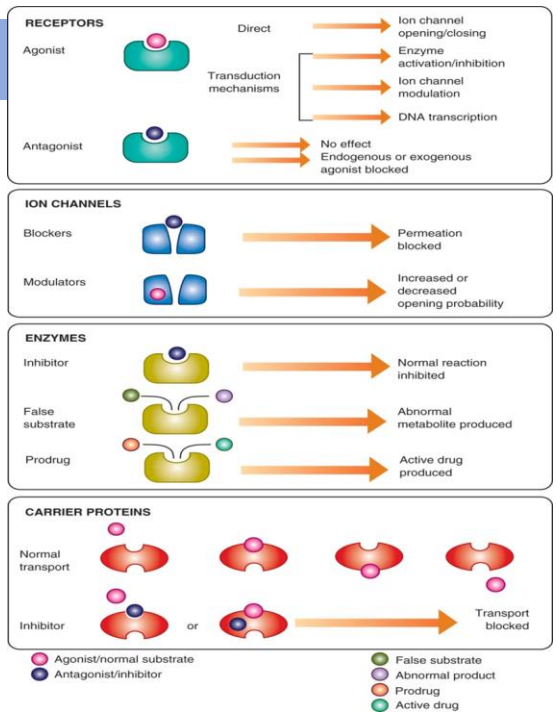
1. **β-adrenergic receptors** that bind and respond to **epinephrine** or **norepinephrine**.
2. **Muscarinic receptors** that bind and respond to **acetylcholine**.

## The drug–receptor complex

- The **magnitude** of the cellular response is **proportional** to the **number of drug–receptor complexes**.
- This concept is conceptually similar to the formation of complexes between **enzyme and substrate** and shares many common features, such as specificity of the receptor for a given agonist.
- 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 with one another, usually favoring **the inactive state**.
- **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.



## Receptor states

- 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*.

## 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.
- However, the richest sources of receptors are **membrane-bound proteins** that transduce extracellular signals into intracellular responses.

## Major receptor families

- These receptors may be divided into four families:

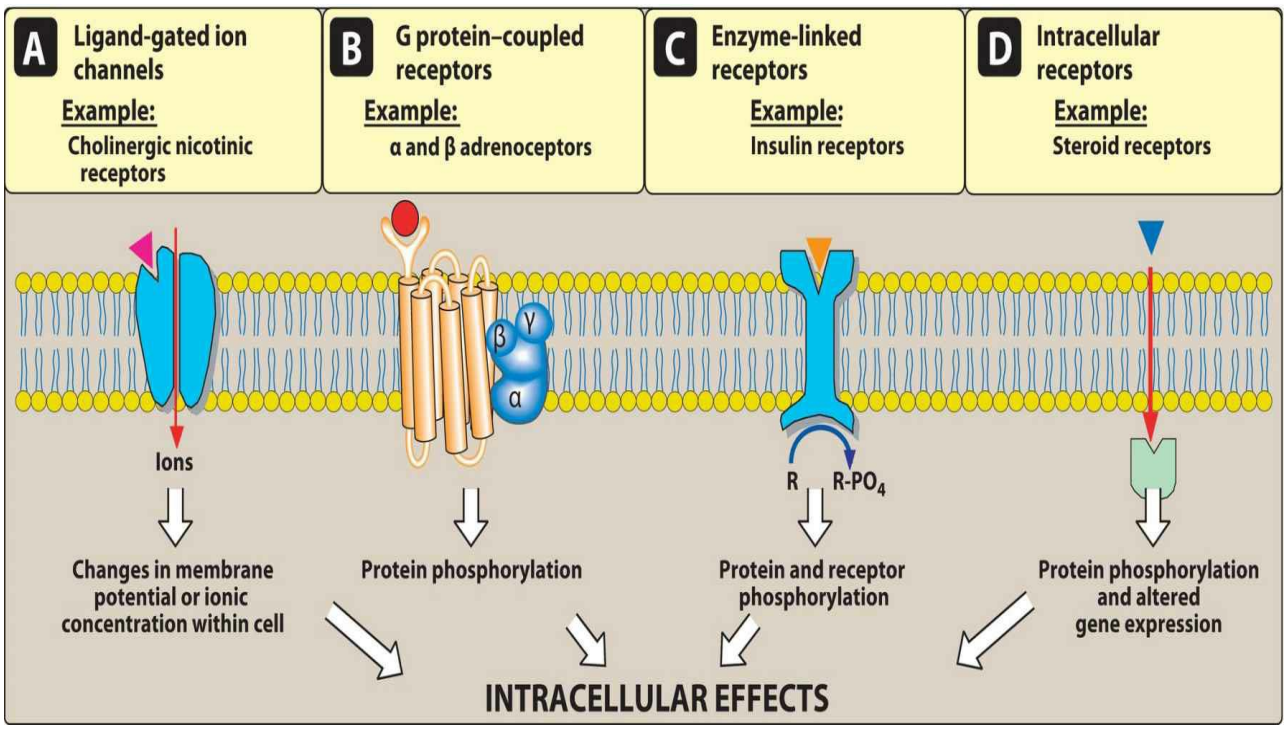
**1) Ligand-gated ion channels**

**2) G protein–coupled receptors**

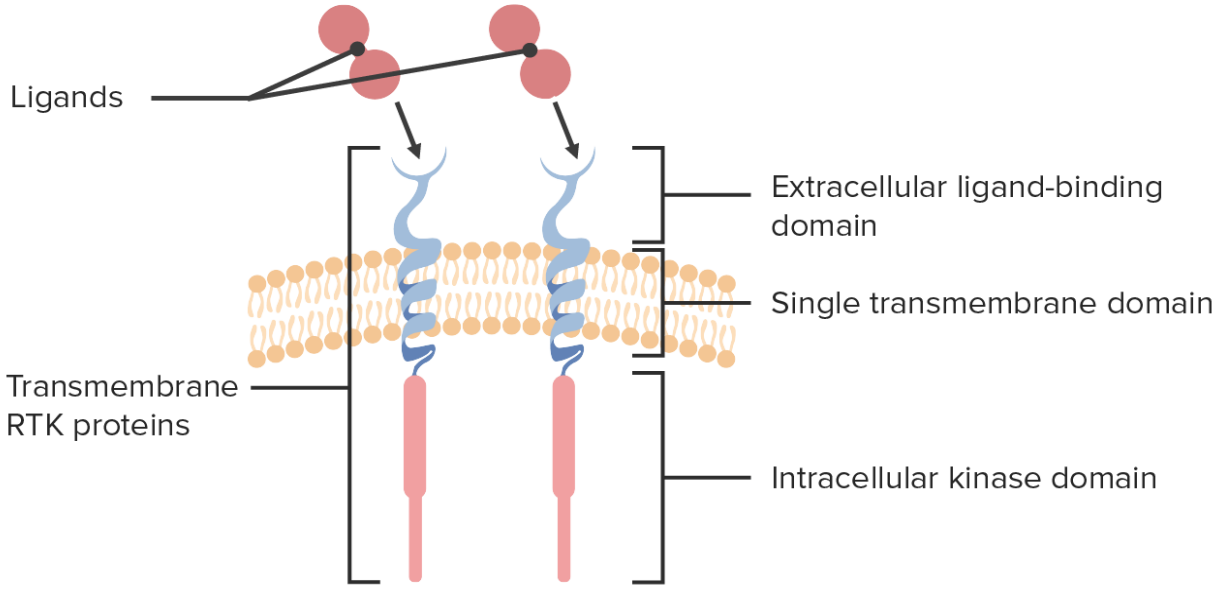
**3) Enzyme-linked receptors**

**4) Intracellular receptors**

- Generally, **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.

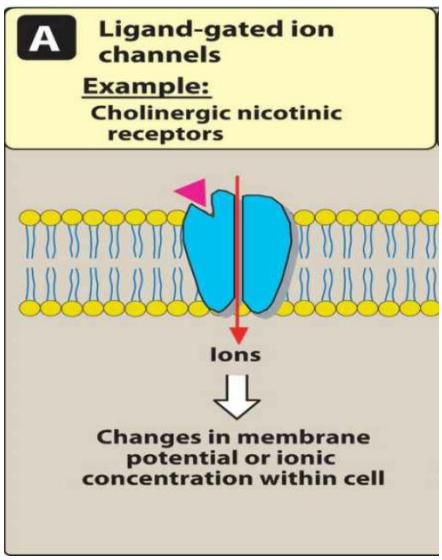


## Receptor structure




## 1. Transmembrane ligand-gated ion channels

- The **extracellular portion** of ligand-gated ion channels contains the **drug-binding site** which regulates the opening 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 for a few **milliseconds**. Depending on the ion conducted through these channels, these receptors mediate diverse functions, including **neurotransmission** and **muscle contraction**.

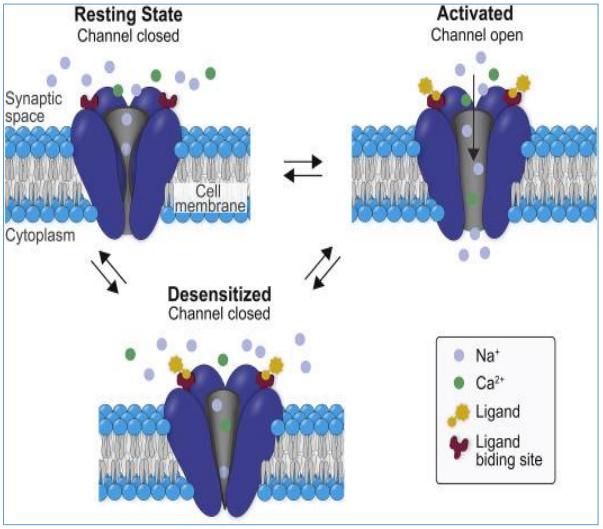


## 1- Transmembrane ligand-gated ion channels

- For example,

1. 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.

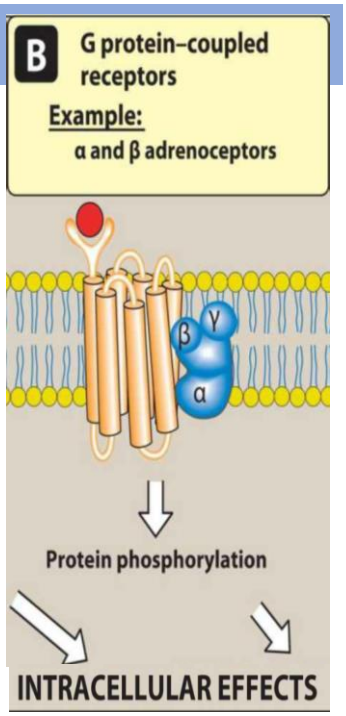
- This change in **ionic concentrations** across the membrane generates an **action potential** in a neuron and **contraction** in skeletal and cardiac muscle.




## 1-Transmembrane ligand-gated ion channels

2. On the other hand, **agonist stimulation of γ-aminobutyric acid (GABA) receptor** increases **chloride influx**, resulting in **hyperpolarization** of neurons and less chance of generating an action potential.
3. **Voltage-gated ion channels may also possess ligand-binding sites that** can regulate channel function. For example, **local anesthetics** bind to the **voltage-gated sodium channel**, inhibiting **sodium influx** and **decreasing neuronal conduction**.

## 2. Transmembrane G protein–coupled receptors

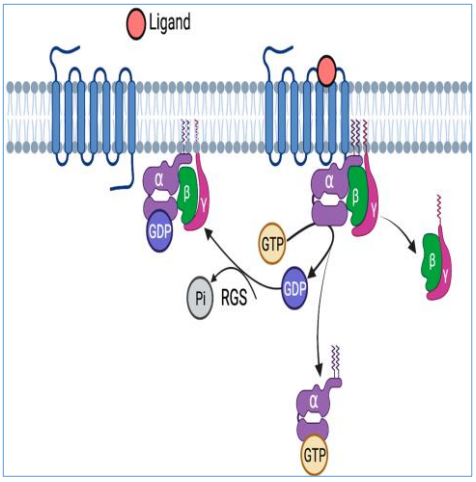



- The **extracellular portion** of this receptor contains **the ligand-binding site**, and the intracellular portion interacts (when activated) with a G protein.
- All types are composed of three protein subunits.

1. The **α subunit** binds guanosine triphosphate (**GTP**), and
2. the **β and γ subunits anchor the G protein** in the cell membrane.

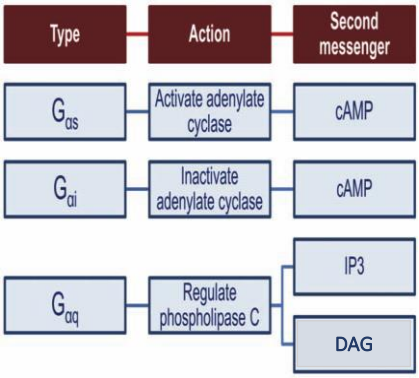
## 2. Transmembrane G protein–coupled receptors

- **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.
- **The α and βγ subunits are then free** to interact with specific cellular effectors, usually an enzyme proteins 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**.



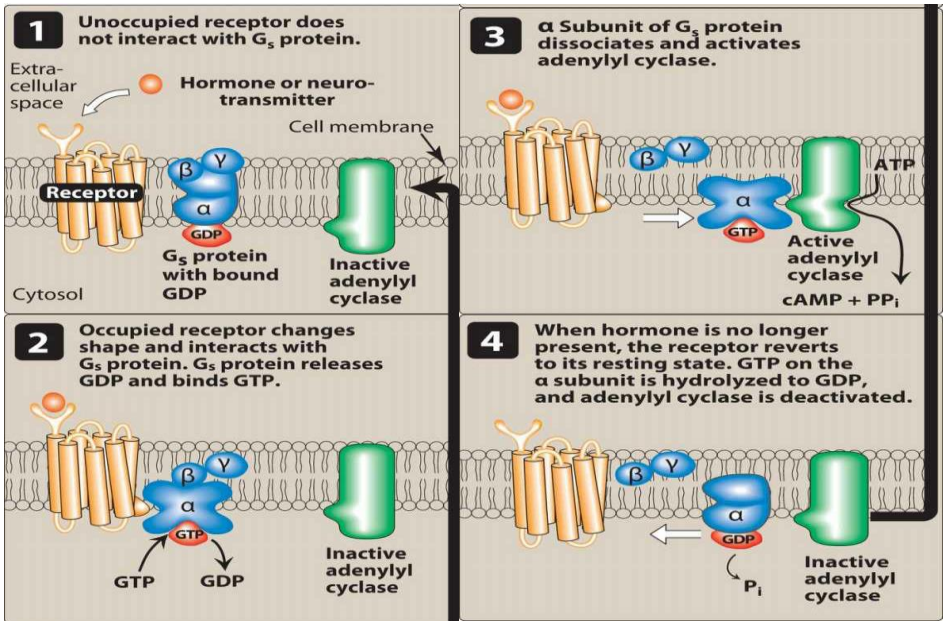
## 2. Transmembrane G protein–coupled receptors

- There are many kinds of G proteins (for example, Gs, Gi, and Gq).
- A common effector, **activated by Gs** and **inhibited by Gi**, is **adenylyl cyclase**, which produces the **second messenger cyclic adenosine monophosphate (cAMP).**
- The **effector phospholipase C**, when activated by Gq, generates two second messengers: **inositol 1,4,5-trisphosphate (IP3)** and **diacylglycerol (DAG).**
- DAG and cAMP activate specific protein kinases within the cell, leading to a myriad of physiological effects.
- **IP3** increases intracellular **calcium concentration**, which in turn activates other protein kinases.



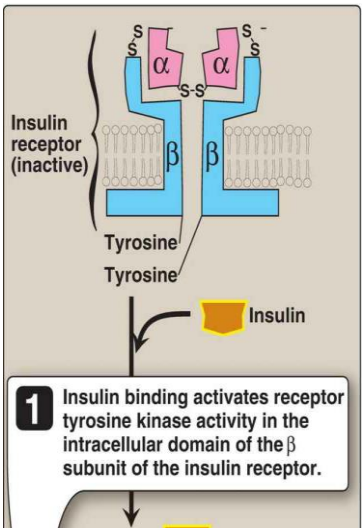

## 2. Transmembrane G protein–coupled receptors

The recognition of chemical signals by G protein–coupled membrane receptors affects the activity of adenylyl cyclase. PPi = inorganic pyrophosphate.



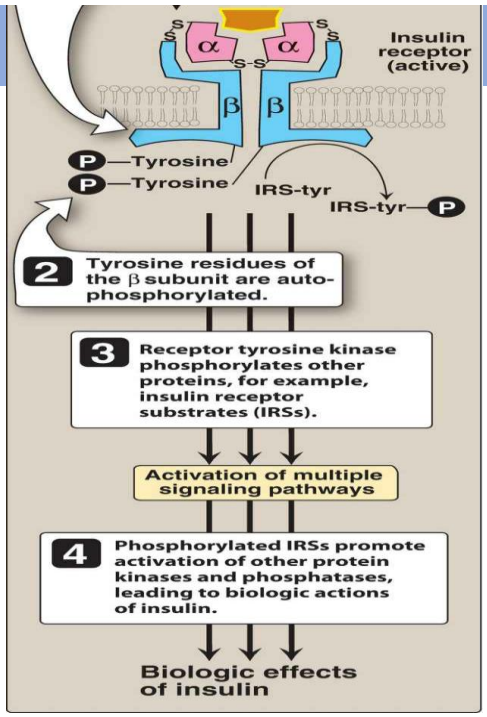
## 3. Enzyme-linked receptors

- This family of receptors consists of a **protein** that may form dimers or multisubunit complexes.
- When activated, these receptors undergo conformational changes resulting in **increased cytosolic enzyme activity**, depending on their structure and function
- This response **lasts for minutes to hours.**
- The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, atrial natriuretic peptide, insulin, and others) possess **tyrosine kinase activity** as part of their structure.
- The activated receptor **phosphorylates tyrosine residues** on itself and other specific proteins.
- Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch.



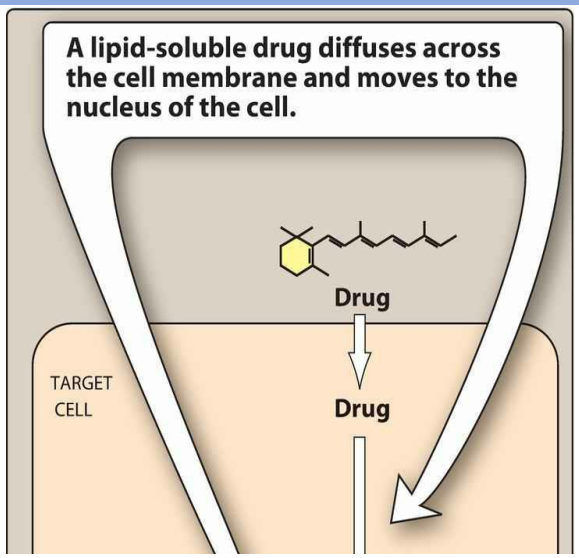

## 3. Enzyme-linked receptors

- 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.



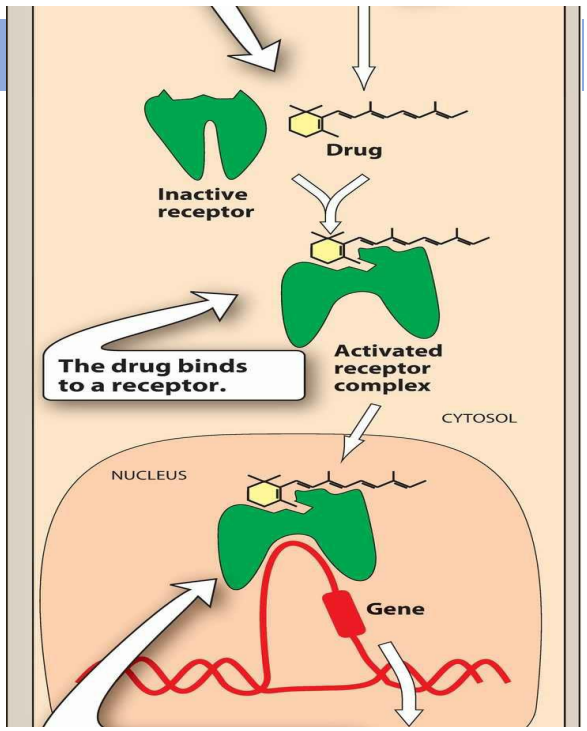
## 4. Intracellular receptors

- The fourth family of receptors differs 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.
- The **primary** targets of ***activated intracellular receptors*** are **transcription factors** in the cell **nucleus**.



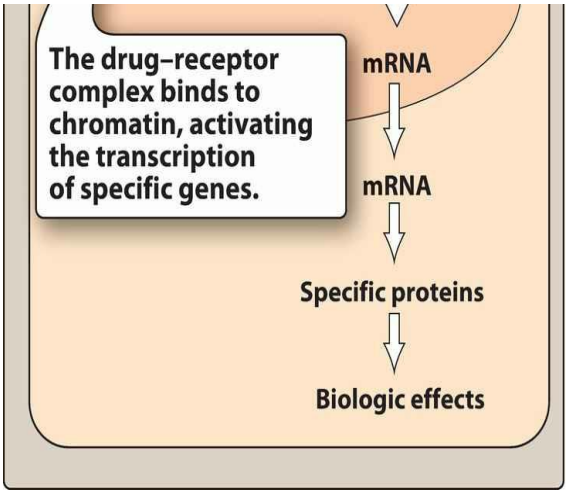

## 4. Intracellular receptors

- Binding of the ligand with its receptor generally **activates the receptor** via **dissociation** from a variety of binding proteins.
- The **activated ligand–receptor complex** then translocates to the nucleus, where it often **dimerizes** before binding to **transcription factors** that **regulate gene expression**.



## 4. Intracellular receptors

- The activation or inactivation of transcription factors alters the **transcription of DNA into RNA** and subsequently translation of RNA into proteins.
- The time course of activation and response of these receptors is on the **order of hours to days.**
- For examples, **Steroid hormones** exert their action on target cells via intracellular receptors.




## 4. Intracellular receptors

- **Other targets of intracellular ligands** are structural proteins, enzymes, RNA, and ribosomes. For example,

1. **Tubulin** is the target of **antineoplastic** agents such as **paclitaxel**
2. **The enzyme dihydrofolate reductase** is the target of **antimicrobials** such as **trimethoprim**
3. **The 50S subunit of the bacterial ribosome** is the target of **macrolide** antibiotics such as **erythromycin**.

## D. Characteristics of signal transduction

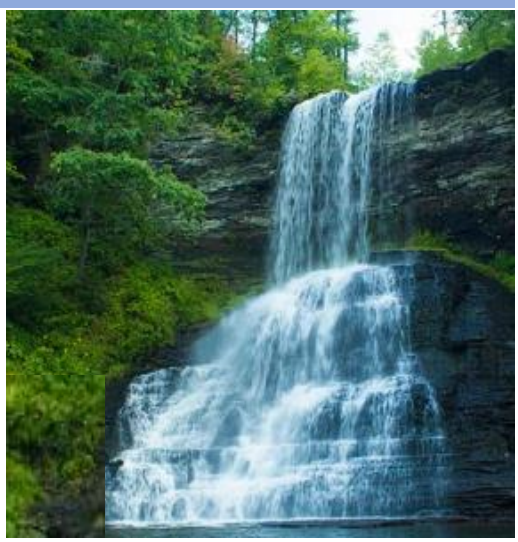
- **Signal transduction has two important features:**

1) the ability to amplify small signals (**Signal amplification**)

2) mechanisms to protect the cell from excessive stimulation (**Desensitization and down-regulation of receptors**)

## 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.
- ***Albuterol*** binding only exist for a few milliseconds, but the activated G proteins last for **hundreds of milliseconds**.



## 1. Signal amplification

- 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**.

1. **99% of insulin receptors are "spare,"** providing an immense functional reserve that ensures that adequate amounts of glucose enter the cell.
2. **5% to 10% of the total β-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.

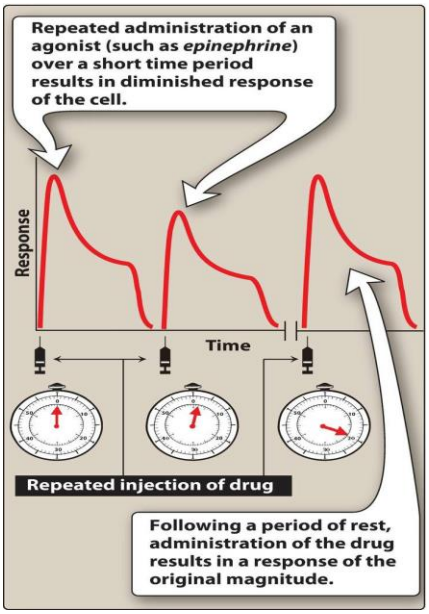
## 2. Desensitization and down-regulation of receptors

- **Repeated** or **continuous** administration of an agonist or antagonist often leads to changes in the responsiveness of the receptor.
- **Tachyphylaxis** is receptor desensitization due to too much **agonist** stimulation, resulting in a diminished response.
- **Tachyphylaxis is often due to**

1. **Phosphorylation** that renders receptors unresponsive.
2. **Receptors internalized** within the cell, making them unavailable for agonist interaction (down-regulation).

## 2. Desensitization and down-regulation of receptors

- Some receptors, particularly ion channels, require a predictable **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 Relationships

- **Agonist drugs** mimic ( **يقلد** ) the action of the endogenous ligand for the receptor ( isoproterenol mimics norepinephrine on β1 receptors of the heart).
- **The magnitude of the drug effect depends** on

**1) Receptor sensitivity to the drug and**

**2) The drug concentration at the receptor site**,

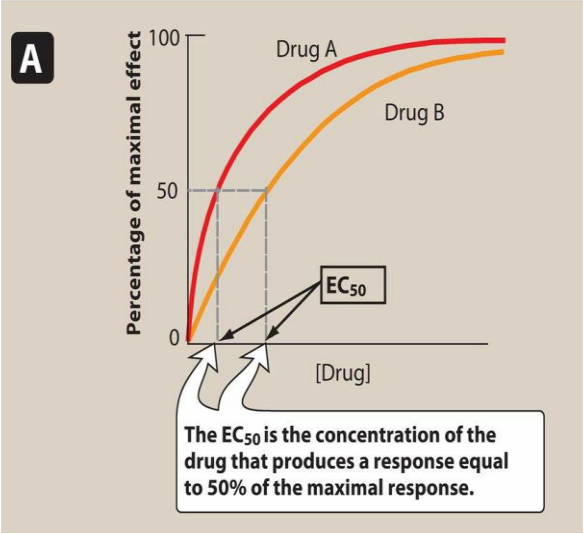
- **The drug concentration at the receptor site** is determined by

1)**The dose of drug administered** and

2)**The drug's pharmacokinetic profile**, such as rate of absorption, distribution, metabolism, and elimination.

## Graded dose–response relationship

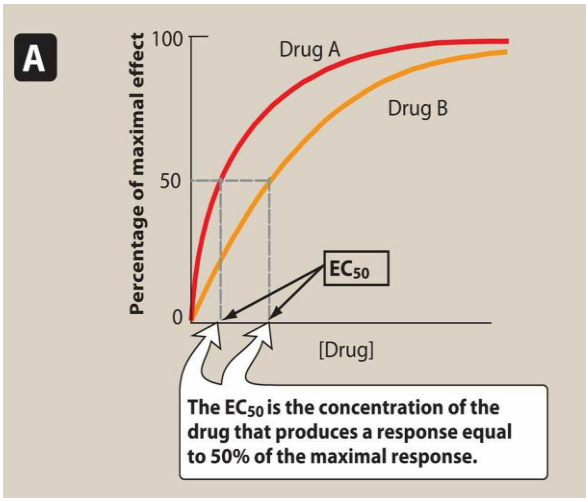
- As the **concentration of a drug increases**, its pharmacologic effect also gradually increases until all the receptors are occupied (**the maximum effect**).
- Plotting the magnitude of response against increasing doses of a drug produces **a graded dose–response curve**. Two important drug characteristics, **potency** and **efficacy**, can be determined.




The effect of dose on the magnitude of pharmacologic response. Panel A is a linear plot.

## 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.
- 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.

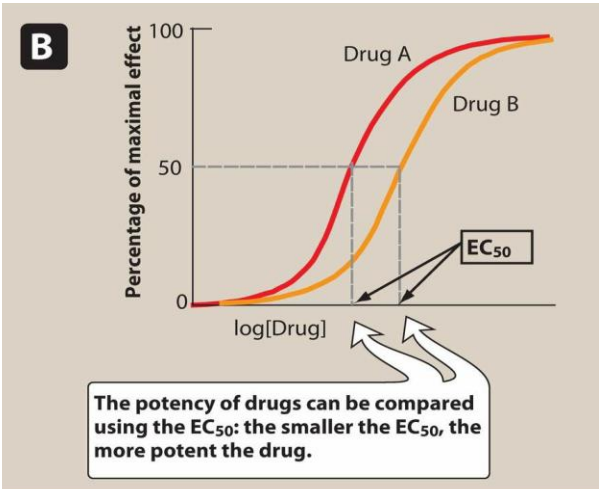



The effect of dose on the magnitude of pharmacologic response. Panel A is a linear plot.

## 1. Potency

- **Therapeutic preparations** of drugs reflect their potency. ***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***.
- As shown in Figure, the curves become **sigmoidal in shape**, which **simplifies** the interpretation of the dose–response curve.



## 2. Efficacy

- Efficacy is **the magnitude of response** a drug causes when it interacts with a receptor.

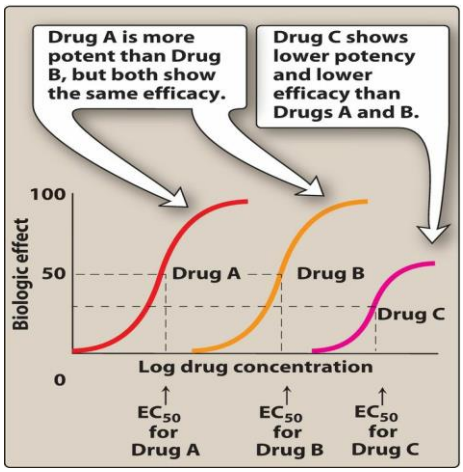
- **Efficacy is dependent on**

1. The **number of drug–receptor complexes formed**

2. **The intrinsic activity of the drug** (its ability to activate the receptor and cause a cellular response).

## 2. Efficacy

- **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, an **antagonist** occupies 100% of the receptors, no receptor activation results and Emax is zero.
- **Efficacy** is a *more clinically useful than potency*, since 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. EC50 = drug dose that shows 50% of maximal response.

## Intrinsic Activity

- An agonist binds to a receptor and produces a biologic response based on the concentration of the agonist, its affinity for the receptor and, hence, the fraction of occupied receptors.
- However, the **intrinsic activity** of a drug further ***determines its ability to fully or partially activate the receptors***.
- Drugs may be categorized according to **their intrinsic activity** and resulting **Emax values**.

## 1- 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**.
- Full agonists bind to a receptor, stabilizing the receptor in its active state and are said to have an ***intrinsic activity of one.***
- **All full agonists** for a **receptor population** should produce the **same Emax**.
- For example, **phenylephrine** is a **full agonist** at α1-adrenoceptors, because it produces the same Emax as the endogenous ligand, **norepinephrine.**

## 1-Full agonists

- Upon binding to α1-adrenoceptors on vascular smooth muscle, both norepinephrine and phenylephrine stabilize the receptor in its active state, thereby increasing Gq activation.
- Activation of Gq increases **intracellular Ca2+,** causing interaction of actin and myosin filaments and shortening of the muscle cells. The diameter of the arteriole decreases, causing an increase in resistance to blood flow through the vessel and an increase in blood pressure.

## 1-Full agonists

- As this brief description illustrates, an agonist may have many measurable effects, including actions on intracellular molecules, cells, tissues, and intact organisms.
- All of these actions are **attributable** to interaction of the **drug** with the **receptor**.
- For full agonists, the dose–response curves for receptor binding and each of the biological responses should be comparable.

## 2-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.
- Even so, a partial agonist may have **an affinity** that is greater than, less than, or equivalent to that of a full agonist.
- ***When a receptor is exposed to both a partial agonist and a full agonist***,

✓the **partial agonist** may act as an **antagonist** of the full agonist.

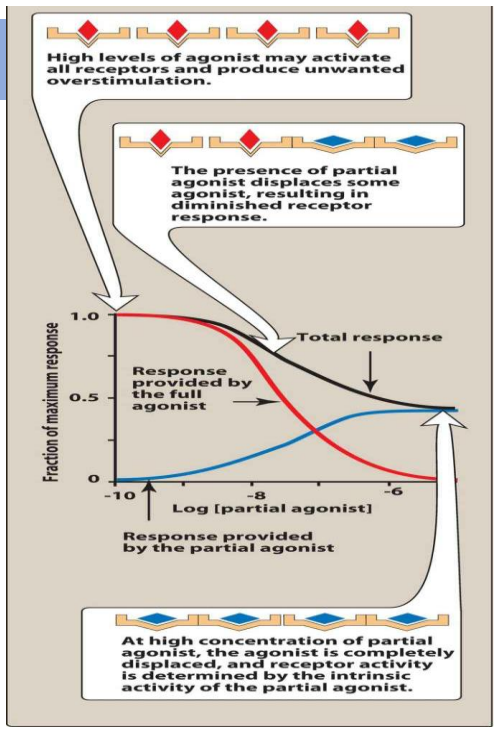
## 2-Partial agonists

- Consider what would happen to the **Emax of a receptor saturated with an agonist** in the presence of **increasing concentrations of a partial agonist**.
- As the number of receptors occupied by the partial agonist increases**, the Emax would decrease** until it reached the Emax of the partial agonist.
- This potential of partial agonists to act as both an agonist and antagonist may be **therapeutically utilized**.

## 2-Partial agonists

- **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.

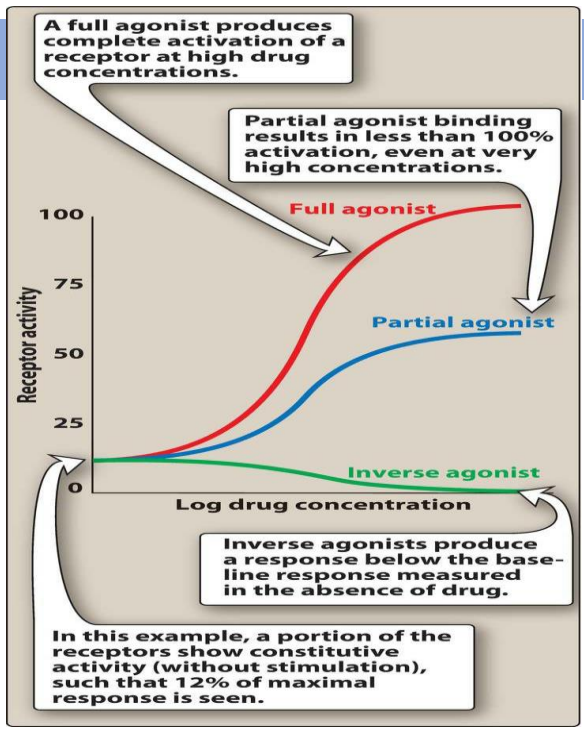

- Effects of partial agonists

## 3-Inverse agonists

- Typically, unbound receptors are inactive and require interaction with an agonist to assume an active conformation.
- However, ***some receptors show a spontaneous conversion from R to R* in the absence of an agonist***.
- **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**, reverse the activation state of receptors, and exert the opposite pharmacological effect of agonists.

- Effects of full agonists, partial agonists, and inverse agonists on receptor activity.



## 4-Antagonists

- Antagonists bind to a receptor with high affinity but **possess zero intrinsic activity.**
- An antagonist has no effect on biological function in the absence of an agonist, but can decrease the effect of an agonist when present.
- **Antagonism** may occur either by blocking the drug's ability to bind to the receptor or by blocking its ability to activate the receptor.

**A. Competitive antagonists**

**B. Irreversible antagonists**

**C. Allosteric antagonists**

**D. Functional antagonism**

## A. Competitive antagonists

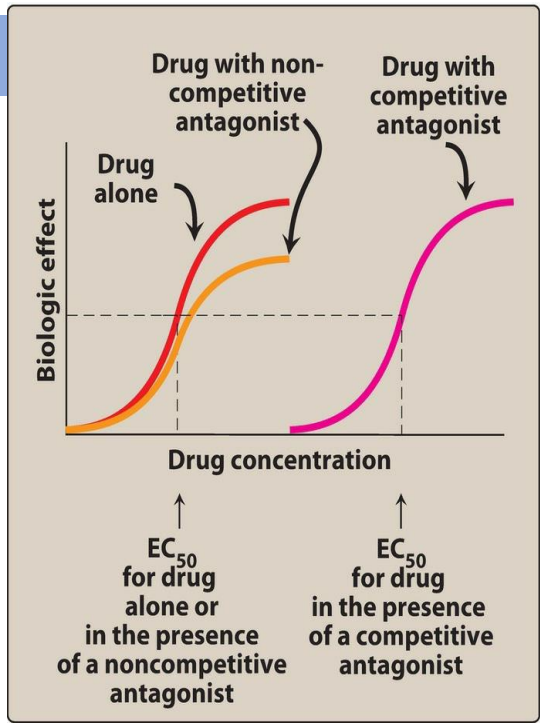
- If the antagonist binds to the same site on the receptor as the agonist, it is "**competitive**."
- **A competitive antagonist** interferes with an agonist binding to its receptor and maintains the receptor in **its inactive state**.
- For example, the antihypertensive drug **terazosin** competes with the endogenous ligand **norepinephrine** at α1-adrenoceptors, thus decreasing vascular smooth muscle tone and reducing blood pressure.
- 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 EC50) without affecting Emax.

## B. Irreversible antagonists

- **Irreversible antagonists** bind **covalently** to the active site of the receptor, thereby permanently reducing the number of receptors available to the agonist.
- An irreversible antagonist causes **a downward shift of the Emax**, with **no shift of EC50 values**.
- In contrast to competitive antagonists, addition of more agonist does not overcome the effect of irreversible antagonists.
- Thus, irreversible antagonists and allosteric antagonists (see below) are both considered **noncompetitive antagonists**. A fundamental difference between competitive and noncompetitive antagonists is that **competitive antagonists** reduce agonist **potency** (increase EC50) and **noncompetitive antagonists** reduce agonist **efficacy** (decrease Emax).

## C. Allosteric antagonists

- An allosteric antagonist binds to a site (allosteric site) other than the agonist-binding site and prevents receptor activation by the agonist.
- This type of antagonist also causes **a downward shift of the Emax** of an agonist, **with no change in the EC50 value**.
- An example of an allosteric agonist is **picrotoxin**, which binds to the inside of the GABA controlled chloride channel. When picrotoxin binds inside the channel, no chloride can pass through the channel, even when GABA fully occupies the receptor.




- **Figure 2.13** Effects of drug antagonists. EC50 = drug dose that shows 50% of maximal response.

## D. 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 H1 **histamine** receptors on bronchial smooth muscle, causing **bronchoconstriction** of the bronchial tree. **Epinephrine** is an agonist at β2-adrenoceptors on bronchial smooth muscle, which causes the muscles to **relax**. This functional antagonism is also known as "physiologic antagonism."

## V. Quantal Dose–Response Relationships

- 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***.
- These responses are known as **quantal responses**, because, for any individual, either the effect occurs or it does not.
- Graded responses can be transformed to quantal responses by designating a predetermined level of the graded response as the point at which a response occurs or not.

## V. Quantal Dose–Response Relationships

- For example, a quantal dose–response relationship can be determined in a population for the antihypertensive drug ***atenolol.***
- A positive response is defined as a fall of at least **5 mm Hg in diastolic blood** pressure.
- 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.

## A. Therapeutic index

- The therapeutic index (TI) of a drug is the ratio of the dose that produces toxicity in half the population (TD50) to the dose that produces a clinically desired or effective response (ED50) in half the population:

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

- The **TI 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.

## 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.
- Although ***high TI values are required for most drugs, some drugs with low therapeutic indices are routinely used to treat serious diseases.***
- In these cases, the risk of experiencing adverse effects is not as great as the risk of leaving the disease untreated.

**1. *Warfarin* (example of a drug with a small therapeutic index)**

- As the dose of *warfarin* is increased, a greater fraction of the patients respond (for this drug, the desired response is a two- to threefold increase in the international normalized ratio [INR]) until, eventually, all patients respond (A). However, at higher doses of *warfarin*, anticoagulation resulting in hemorrhage occurs in a small percent of patients. **Agents with a low TI** (that is, drugs for which dose is critically important) are those drugs for which **bioavailability critically alters the therapeutic effects**.

**2. *Penicillin* (example of a drug with a large therapeutic index)**

- For drugs such as *penicillin* (B), 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. In this case, **bioavailability does not critically alter the therapeutic or clinical effects.**

- Cumulative percentage of patients responding to plasma levels of *warfarin* and *penicillin*. Figure shows the responses to warfarin, an oral anticoagulant with a low TI, and penicillin, an antimicrobial drug with a large TI.