

# Pharmacodynamic

# Introduction

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

## □ Drug effect

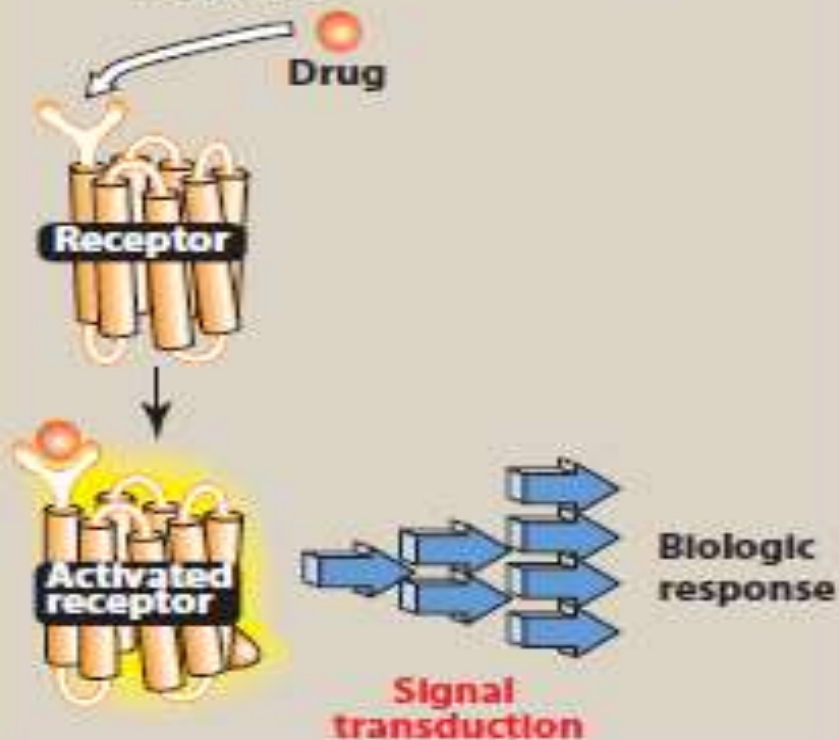
- Drugs bind to specific receptors.
- Receptors activation results in initiating a series of reactions produces specific intracellular response.

**1**

Unoccupied receptor does not influence intracellular processes.

**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.



# 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.
- Cardiac cell membranes, contain  $\beta$  receptors that bind and respond to norepinephrine, and muscarinic receptors specific for acetylcholine.

# Major receptor families

- Receptor is any biologic molecule to which a drug binds and produces a measurable response.
- Most receptors are proteins, Enzymes, nucleic acids.
- **These receptors divided into four families:**
  - 1) ligand-gated ion channels.
  - 2) G protein-coupled receptors.
  - 3) enzyme-linked receptors.
  - 4) intracellular receptors.

# Types of receptors

**A** Ligand-gated ion channels

Example:  
Cholinergic nicotinic receptors

**B** G protein-coupled receptors

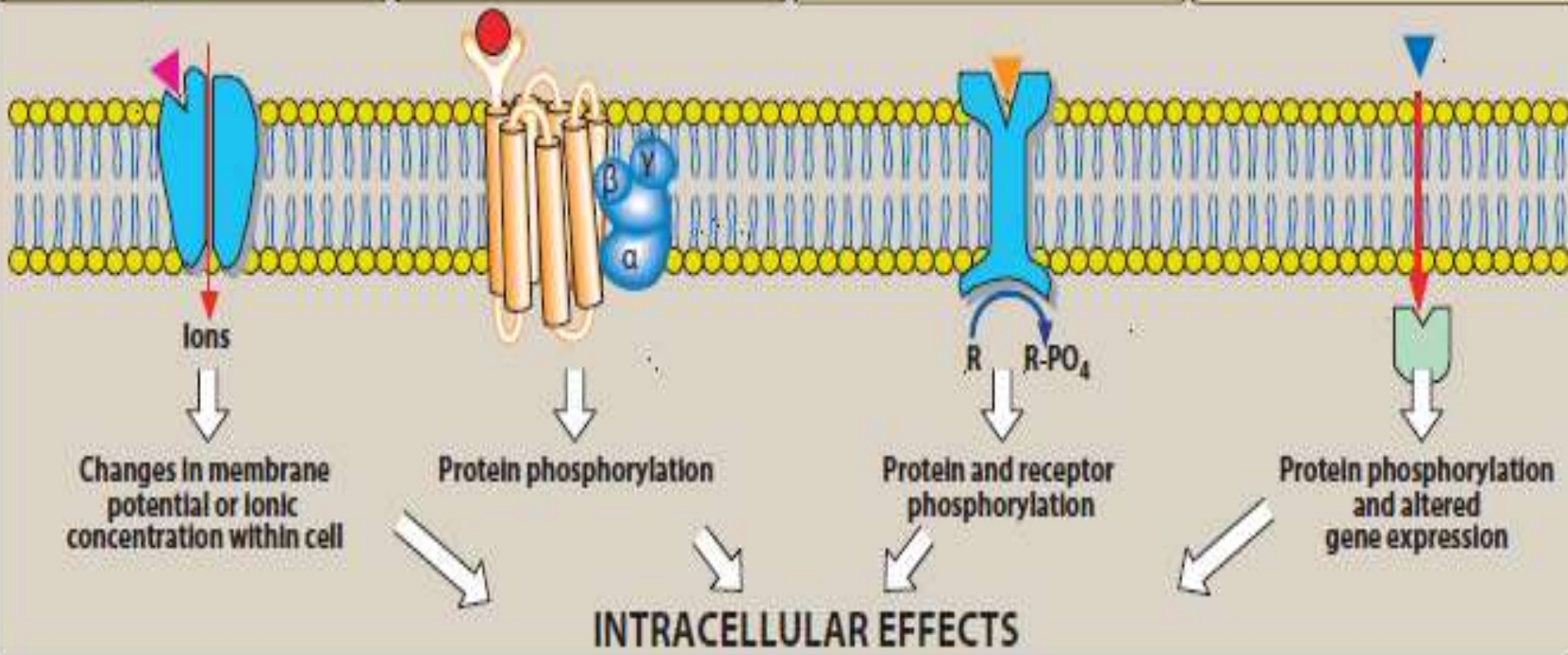
Example:  
 $\alpha$  and  $\beta$  adrenoceptors

**C** Enzyme-linked receptors

Example:  
Insulin receptors

**D** Intracellular receptors

Example:  
Steroid receptors



# 1. Transmembrane ligand-gated ion channels

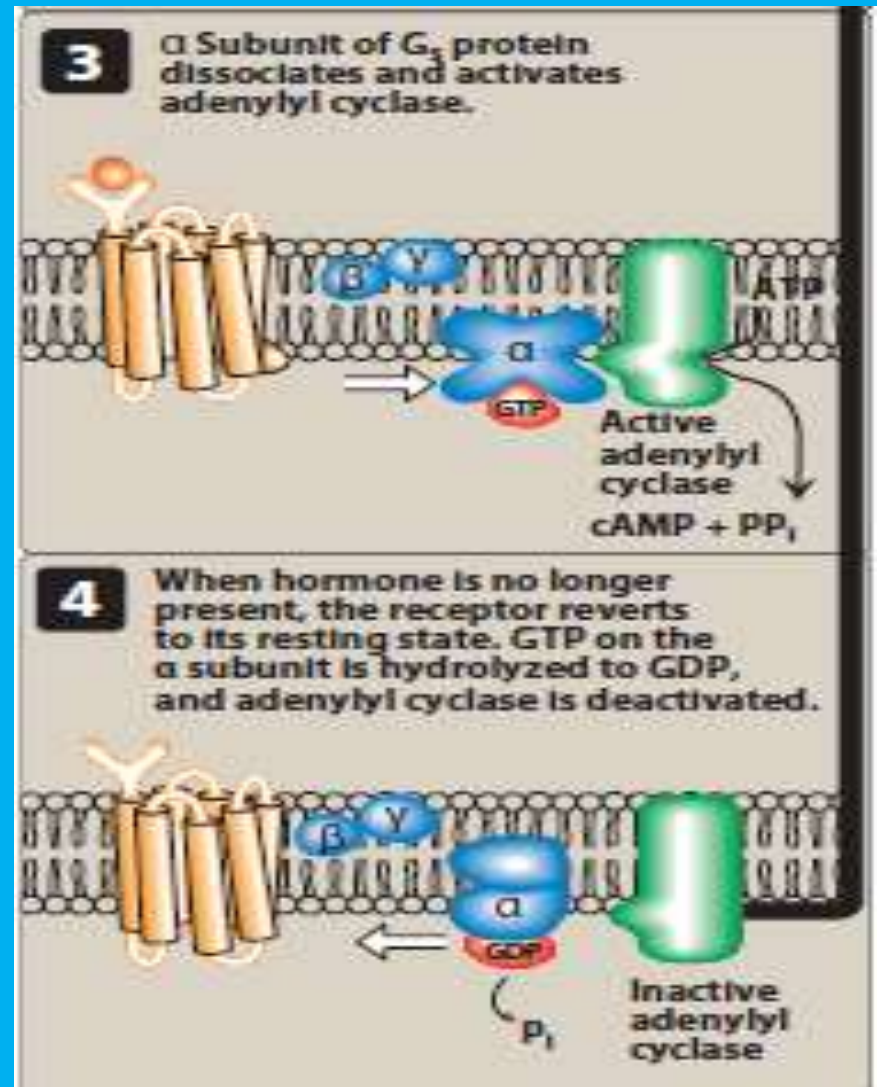
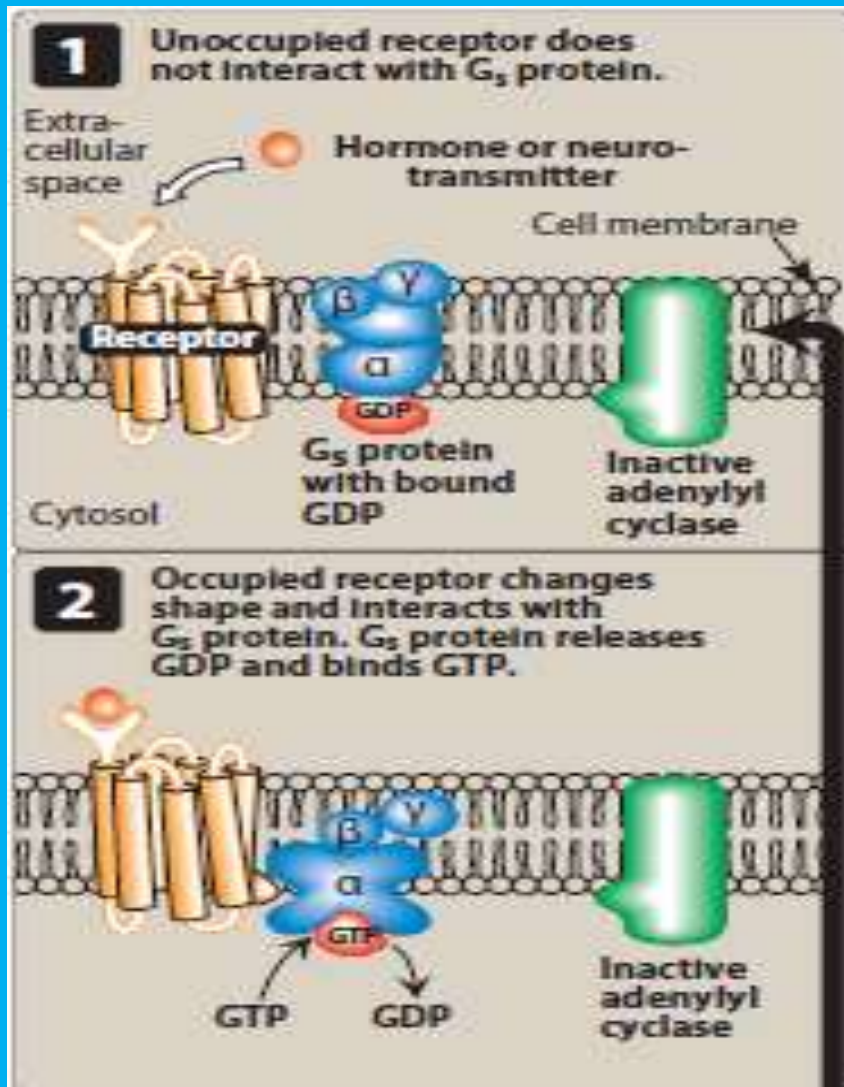
- The extracellular portion of ligand-gated ion channels usually contains the binding site.
- The channel is usually closed until the receptor is activated by an agonist, which opens the channel.
- For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx and potassium outflux.

## 2. Transmembrane G protein–coupled receptors

- The extracellular domain of this receptor contains the binding site, and the intracellular domain interacts with a G protein or effector molecule.
- There are many kinds of G proteins but they all are composed of three protein subunits,  $\alpha$ ,  $\beta$  and  $\gamma$  subunits.
- Upon activation it produce effects.



# Transmembrane G protein-coupled receptors action

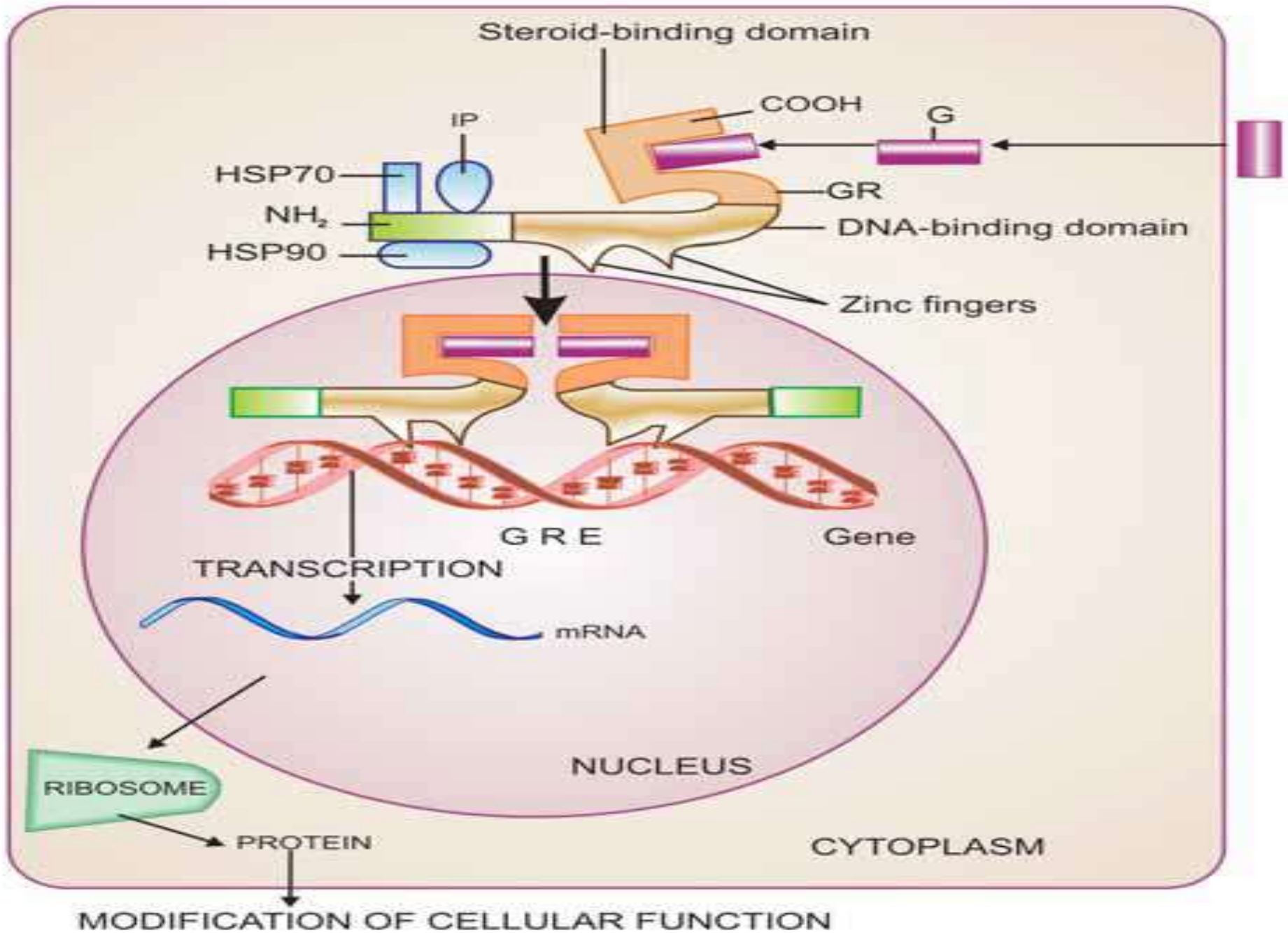


# 3. Enzyme-linked receptors

- This family of receptors consists of a protein.
- When activated, these receptors undergo conformational changes resulting in increased enzyme activity.
- For example, when insulin binds to two of its receptor subunits, causes autophosphorylation of the receptor itself.

## 4. Intracellular receptors

- The fourth family is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor.
- The primary targets of these ligand– receptor complexes is the cell nucleus.
- The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into proteins.



## **Desensitization and down-regulation of receptors**

- When a receptor is exposed to repeated administration of an agonist, the receptor becomes desensitized (tachyphylaxis).
- In addition, receptors may be down-regulated such that they are internalized and sequestered within the cell.

# DOSE-RESPONSE RELATIONSHIPS

□ Dose response relation describes:



## A. Graded dose–response relations

- 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 doses of a drug produces a graded dose–response curve determine two important properties of drugs, **potency and efficacy**.

# 1. Potency

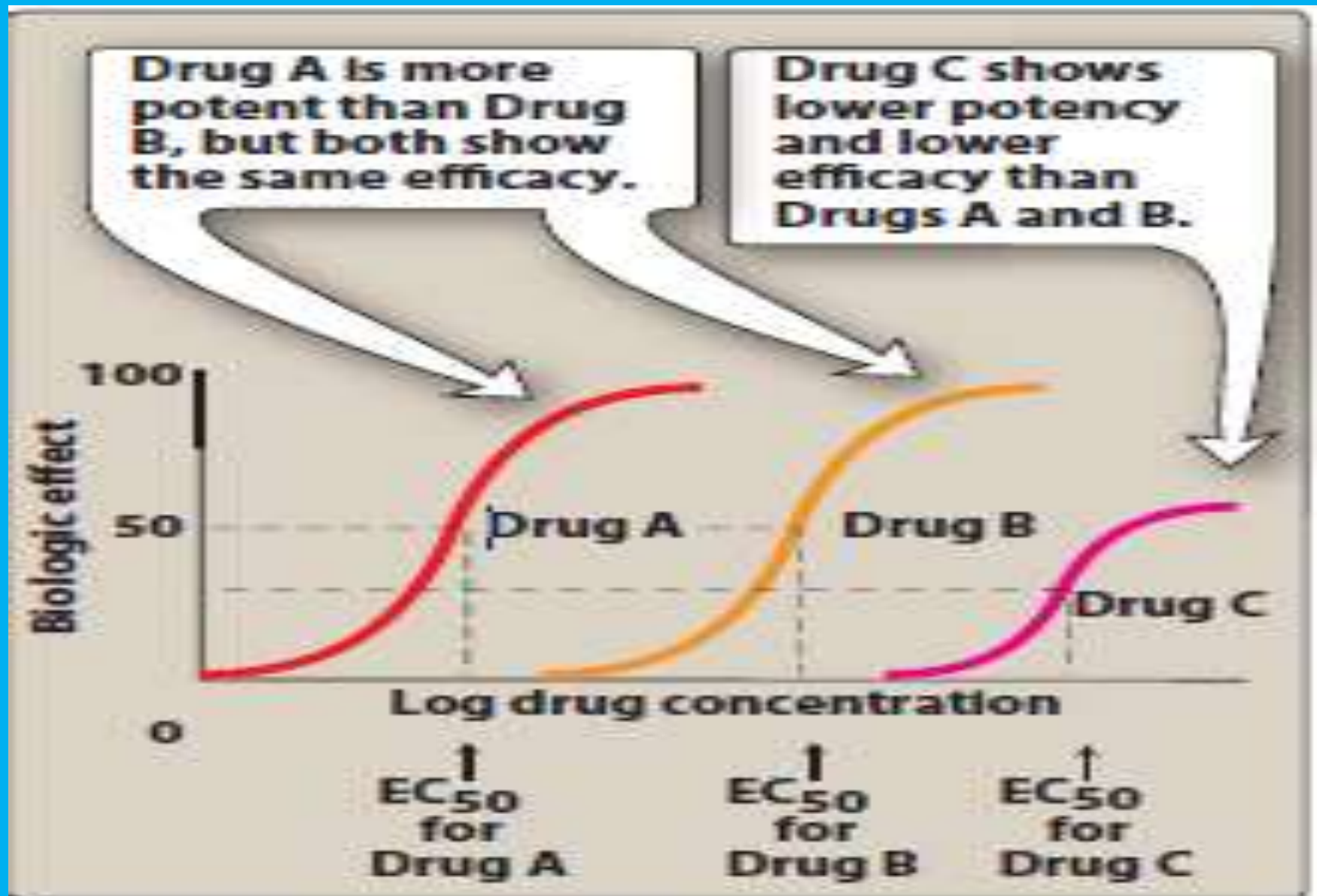
- Potency is a measure of the amount of drug necessary to produce an effect of a given magnitude.
- For example The therapeutic dose range for *candesartan* is 4 to 32 mg, as compared to 75 to 300 mg for *irbesartan*.
- Therefore, *candesartan* is more potent than is *irbesartan* .



## 2. Efficacy

- Efficacy is the magnitude of response a drug causes when it interacts with a receptor.
- Maximal efficacy of a drug ( $E_{max}$ ) assumes that all receptors are occupied by the drug.
- Efficacy is a more clinically useful characteristic than is drug potency.

# Curve of potency and efficacy



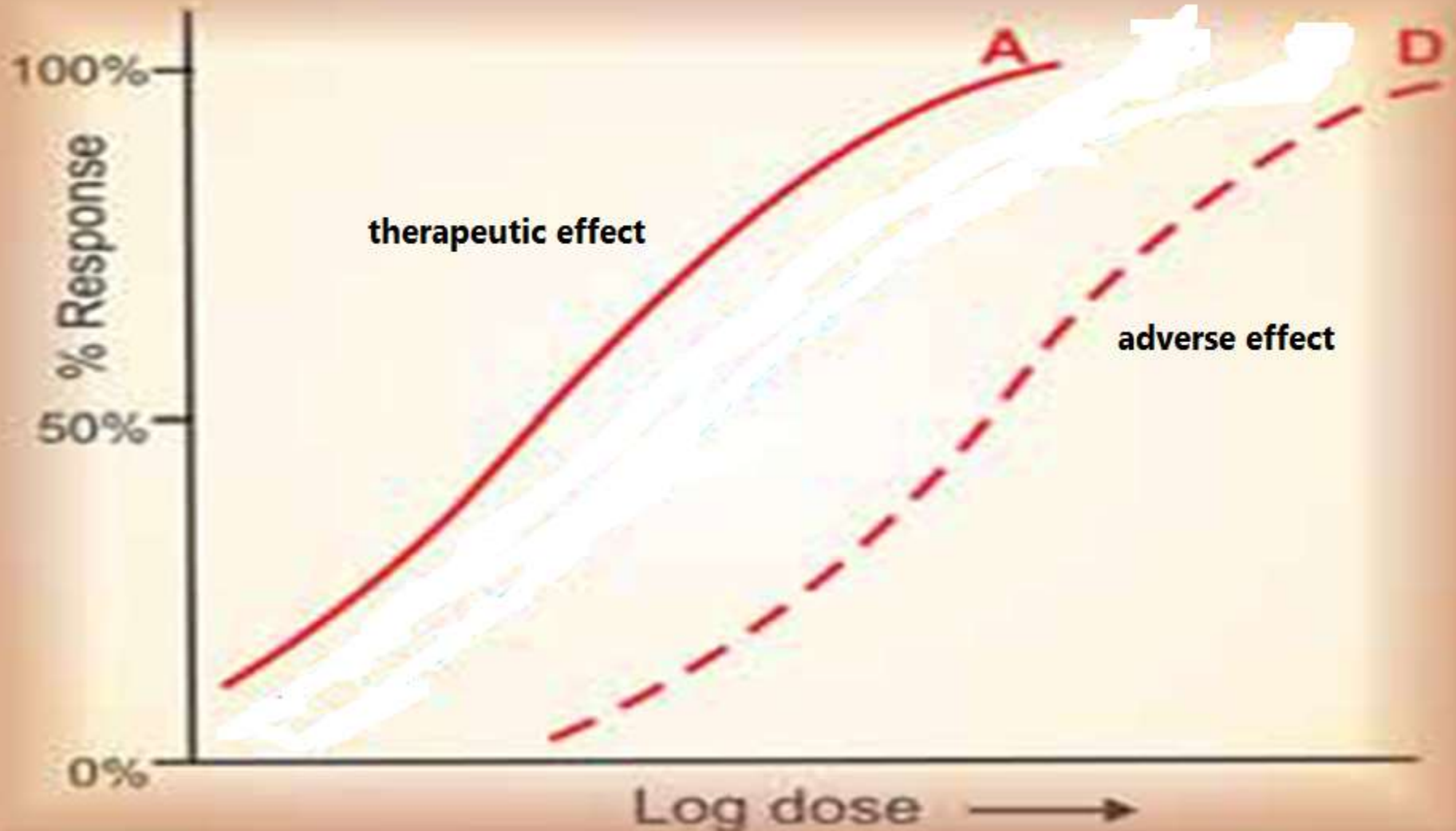
## B. Effect of drug concentration on receptor binding

- As the concentration of free drug increases, more receptors occupied.
- Drug + Receptor  $\longrightarrow$  Drug-receptor complex  $\longrightarrow$  Biologic effect
- This response is related to the percent of receptors occupied.

## C. Relationship of drug binding to pharmacologic effect

- 1) The magnitude of the response is proportional to the amount of receptors occupied,
- 2) The Emax occurs when all receptors are bound.
- 3) The binding of the drug to the receptor exhibits no cooperativity.
- This mean that many drugs can bind to more than one type of receptor, causing both desired therapeutic effects and undesired side effects.

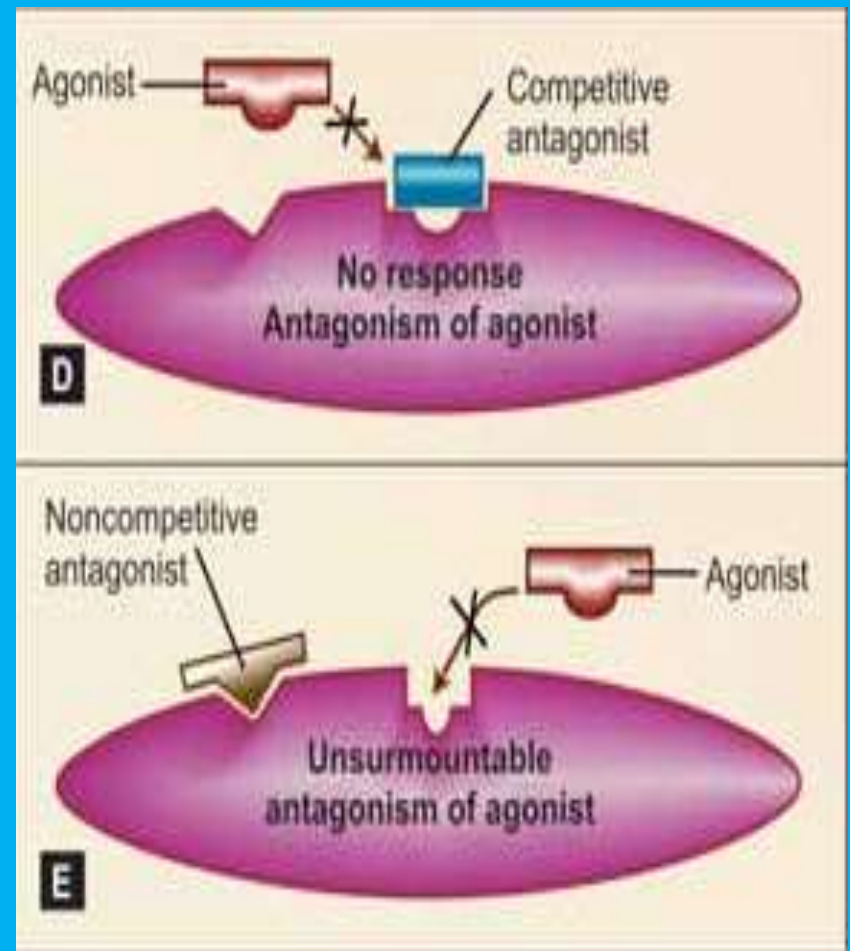
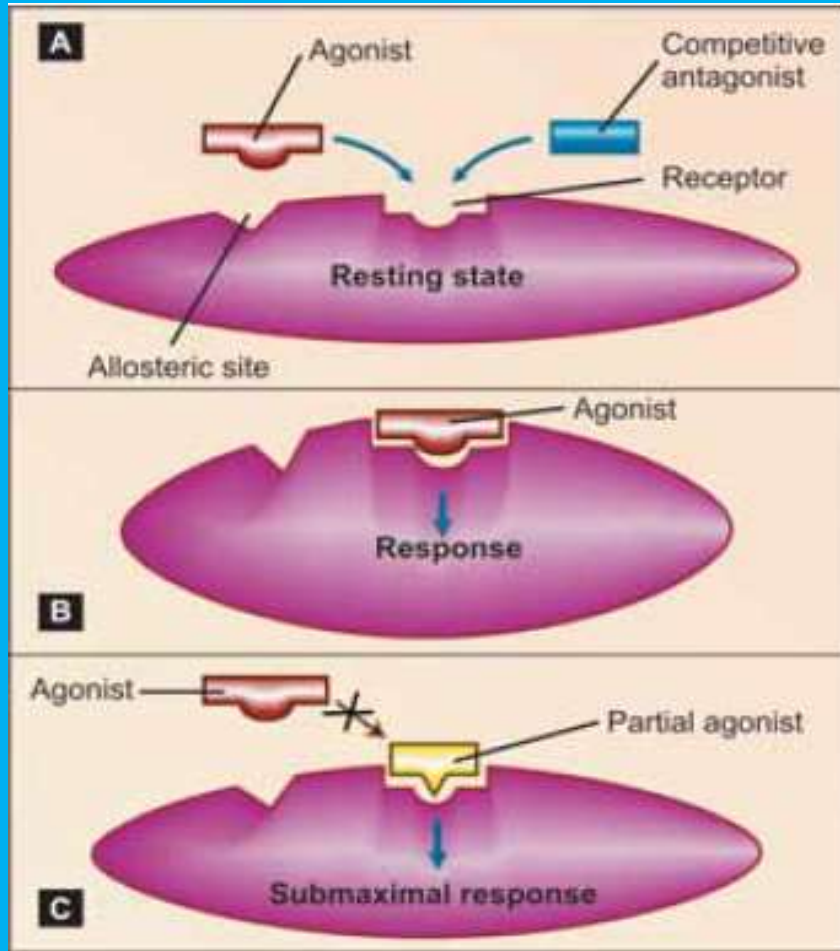
# Illustration of drug selectivity of salbutamol for bronchodilatation(A) and cardiac stimulation (D)



# INTRINSIC ACTIVITY

- The intrinsic activity of a drug determines its ability to activate the receptors.
- **Drugs may be categorized according to their intrinsic activity as:**
  - **A. Full agonists**
  - **B. Partial agonists**
  - **C. Inverse agonists**
  - **D. Antagonists**

# Intrinsic receptor activity



## A. Full agonists

- If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous substance.
- example, *phenylephrine* is a full agonist at  $\alpha_1$ -adrenoceptors.
- Upon binding to  $\alpha_1$ -adrenoceptors on vascular smooth muscle, *phenylephrine* activate the receptor  $\longrightarrow$  increase in blood pressure.



## B. Partial agonists

- Similar to agonist but intrinsic activities less than agonist even if all the receptors are occupied
- When a receptor is exposed to both a partial agonist and a full agonist, the partial agonist may act as an antagonist to the full agonist.

## C. Inverse agonists

- Inverse agonists stabilize the inactive receptor and convert the active to inactive.
- Thus, inverse agonists exert the opposite pharmacological effect of agonists.

# D. Antagonists

- An antagonist has no effect in the absence of an agonist but can decrease the effect of an agonist when present.

## □ Types of antagonism

- **1. Competitive antagonists:**
- Both the antagonist and the agonist bind to the same site on the receptor.
- This inhibition can be overcome by increasing the concentration of agonist relative to antagonist.

## 2. Irreversible antagonists

- Irreversible antagonists bind to the active site of the receptor, thereby reducing the number of receptors available to the agonist.
- The effect of irreversible antagonists cannot be overcome by adding more agonist.
- Thus, it is considered noncompetitive antagonists.

# Difference between competitive and non competitive antagonism

