Mechanism of Drug Action

(Pharmacology), KGMC, Peshawar

Objectives

- Classification of mechanisms of drug action
  - Non-Receptor-Mediated mechanisms
  - Receptor-Mediated mechanisms
- Regulation of receptors
  - Upregulation
  - Downregulation
  - Desensitization

Grossly

1. **Non-Receptor-Mediated** mechanism of action of drugs

    a) Physiochemical Mechanisms
    b) Pharmacological Mechanisms
        i. Intercellular
        ii. Intracellular

2. **Receptor-Mediated** mechanisms of action of drugs

1. Non-Receptor mediated mechanisms of drug action

a) Physiochemical mechanisms

i. *Acids and bases*
ii. *osmotic agents*
iii. *Surfactants*
iv. *Adsorbents*
v. *Physical barriers*
vi. *Astringents*
vii. *Oxidizing and reducing agents*
viii. *Radioactive and radiopaque agents*

1. Non-Receptor mediated mechanisms of drug action

b) Pharmacological mechanisms

A. Intercellular signaling

i. Direct contact
ii. Synapses
iii. Exocrine signals
iv. Endocrine signals

B. Intracellular signaling

i. Receptors*
ii. Ion channels
iii. Enzymes
iv. Carrier molecules

C. Through Antibody Production

D. Transporters

E. Others

2. Receptor-mediated mechanism of drug action

Includes the different types of receptor families

a) Ligand gated ion channels (e.g.cholinergic nicotinic receptors)
b) G-Protein coupled receptors (e.g.alpha and B-receptors)
c) Enzyme linked receptors (e.g.Insulin receptors)
d) Intracellular receptors (e.g.Steroid receptors)

- The targets for G protein are cAMP, Phosphoinositides and Ca++, DAG, cGMP, Ion channels, Arachidonic and metabolites

- *Source: Lipincott Pharmacology - 6th Edition*

Non-Receptor-Mediated Mechanisms

a) Physiochemcial Mechanisms

a) Physiochemcial Mechanisms

- ✓**Acids and Bases:** e.g 1) use of antacids to neutralize the gastric hyperacidity and 2) using sodium bicarbonate and ammonium chloride to increase the urinary excretion of acidic and basic drugs, respectively

- ✓**Osmotic Agents:** e.g. 1) bulk and saline purgatives and 2) osmotic diuretics

- ✓**Surfactants:** e.g. different agents like soaps to disrupt the plasma membrane of micro organisms

a) Physiochemcial Mechanisms

- ✓**Adsorbents:** e.g. use of finely divided substances with large area of adsorption for bacteria, toxins and poisons like kaolin powder for diarrhea and activated charcoal for poisoning.

- ✓**Physical barriers:** Demulcents used to coat the inflamed surface of mucous membrane.

- ✓**Astringents:** Certain hemostatic agents act by precipitating and denaturing protein to stop bleeding.

a) Physiochemcial Mechanisms

- ✓**Oxidizing and reducing agents:** Weak solution of potassium permanganate (0.01%) may be used as oxidizing agent in the treatment of morphine and strychnine still present in the stomach.

- ✓**Radioactive and radiopaque agents:** for ionizing and absorption of radioactive rays for the treatment or diagnosis of disease.

b) Pharmacological mechanisms

1) Intercellular signaling mechanisms

❑**Direct Contact:**

- b/w adjacent cells via communicating junctions b/w cytoplasms of two cells.
- These are composed of special structures called connexons which are bound by six identical proteins arranged in a circle
- Small molecules like aminoacids or sugar and ions can pass through these junctions.

1) Intercellular signaling mechanisms

- **Synapses:**
- the narrow gaps b/w the neurons
- where two neurons communicate with each other
- through release of neurotransmitter by axons

1) Intercellular signaling mechanisms

- **Exocrine signals:**
- Signal molecules released by cells diffuse to other cells through extracellular fluid.

- If destroyed or removed instantaneously
  - the effect is short lived
  - confined to the cells in the immediate vicinity of the releasing cells.

1) Intercellular signaling mechanisms

- **Endocrine signals:**
- released molecules enter the circulatory system from the extracellular fluid

- These effect the cells of the body quite distant from the releasing cells e.g. hormones.

2) Intracellular mechanisms

A. Receptors (discussed leter with receptor mediated mech.)
B. Ion channels
C. Enzymes
D. Carrier molecules

B. Ion Channels

- The ligand gated channels are linked to a receptor and open when the receptor is occupied by a ligand
- Some drugs directly bind to ion channels and alter the flow of ions
- E.g. local anesthetics block sodium channels in neuronal membrane to produce local anesthesia

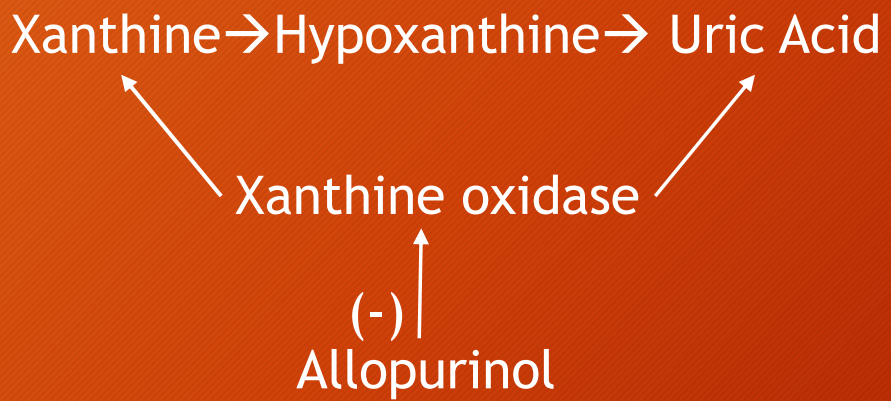
C. Enzymes

- These drugs act on the enzymes either activating or inactivating them.
- E.g. aspirin acting on cyclo-oxygenase, relatively inactivates it by acetylation
- Neostigmine reversibly and competitively inhibits cholinestrase

C. Enzymes…contd.

- Angiotensin converting enzyme (ACE) inhibitors such as captopril, enalapril etc – used in the treatment of HTN, act by inhibiting ACE.

- Xanthine and hyptoxanthine are oxidized to uric acid by enzyme xanthine oxidase, which is inhibited by allopurinol (in the tx of chronic gout to reduce the synthesis of uric acid)



D. Carrier Molecules/Transporters

- Some polar and organic molecules are transported across the cell membrane by a carrier protein.
- The carrier proteins have a recognition site for the particular molecule.
- Sometimes the recognition site acts as a target for the binding drug like Na+K+ ATPase which binds digoxin
- Digoxin inhibits the enzyme after binding with it.

2) Receptor-Mediated-Mechanisms of Drug Action

A. Receptors

2. Receptor-mediated mechanism of drug action

Includes the different types of receptor families

a) Ligand gated ion channels (e.g.cholinergic nicotinic receptors)
b) G-Protein coupled receptors (e.g.alpha and B-receptors)
c) Enzyme linked receptors (e.g.Insulin receptors)
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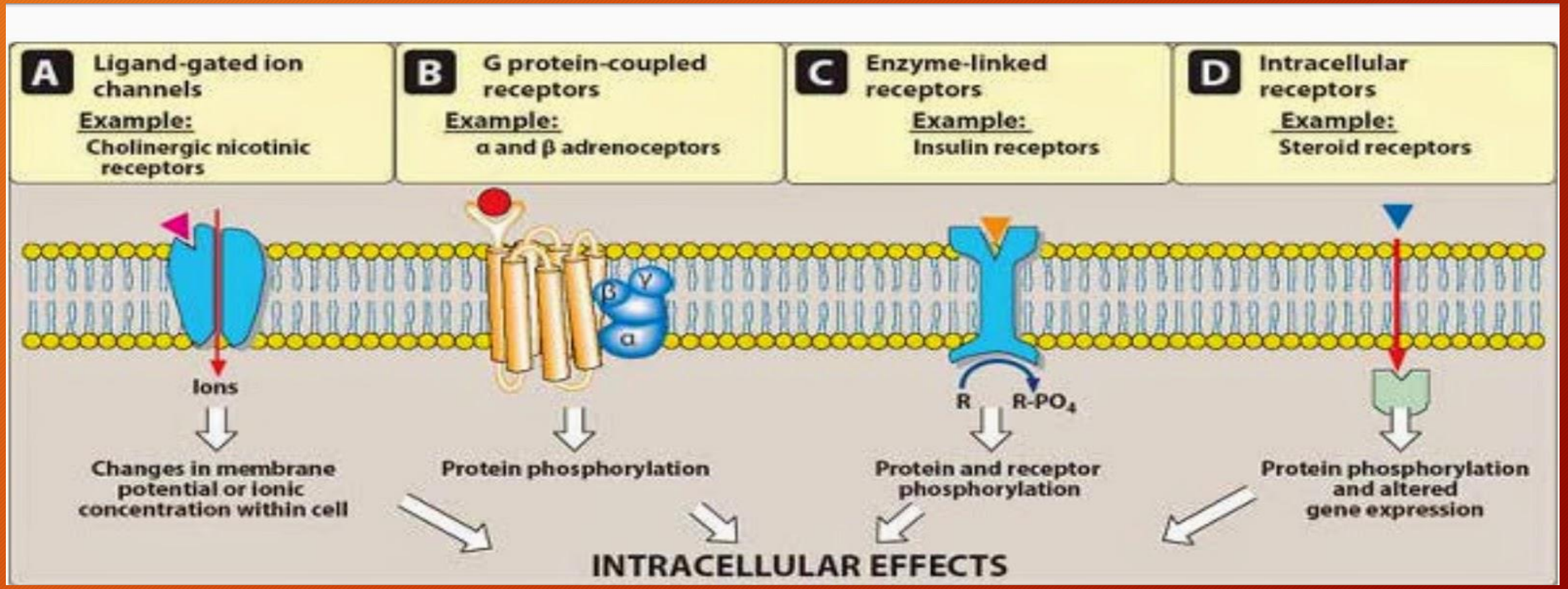
a) Ligand gated ion channels



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

a) Ligand gated ion channels

- Depending on the ion conducted through these channels, these receptors mediate diverse functions, including neurotransmission, and cardiac or muscle contraction.
- E.g. 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.
- On the other hand, agonist stimulation of the γ-aminobutyric acid (GABA) receptor→increases chloride influx and hyperpolarization of neurons.

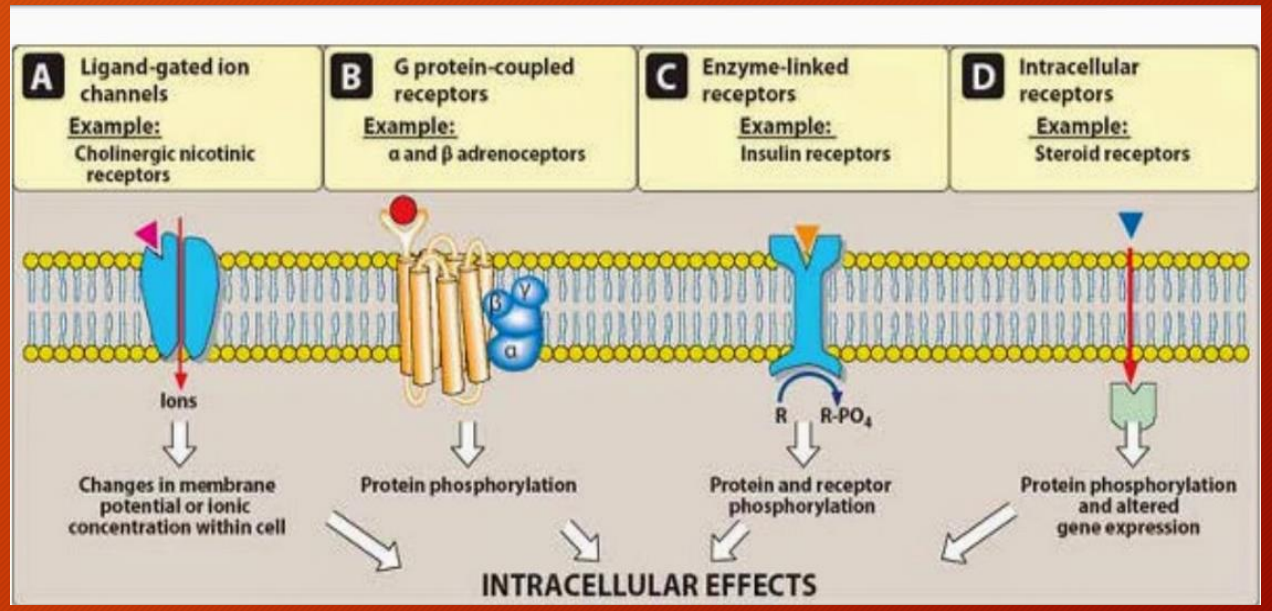
a) Ligand gated ion channels

- Voltage-gated ion channels may also possess ligand-binding sites that can regulate channel function.

- E.g. local anesthetics bind to the voltage-gated sodium channel, inhibiting sodium influx and decreasing neuronal conduction.

b) Transmembrane G-Protein Coupled Receptors

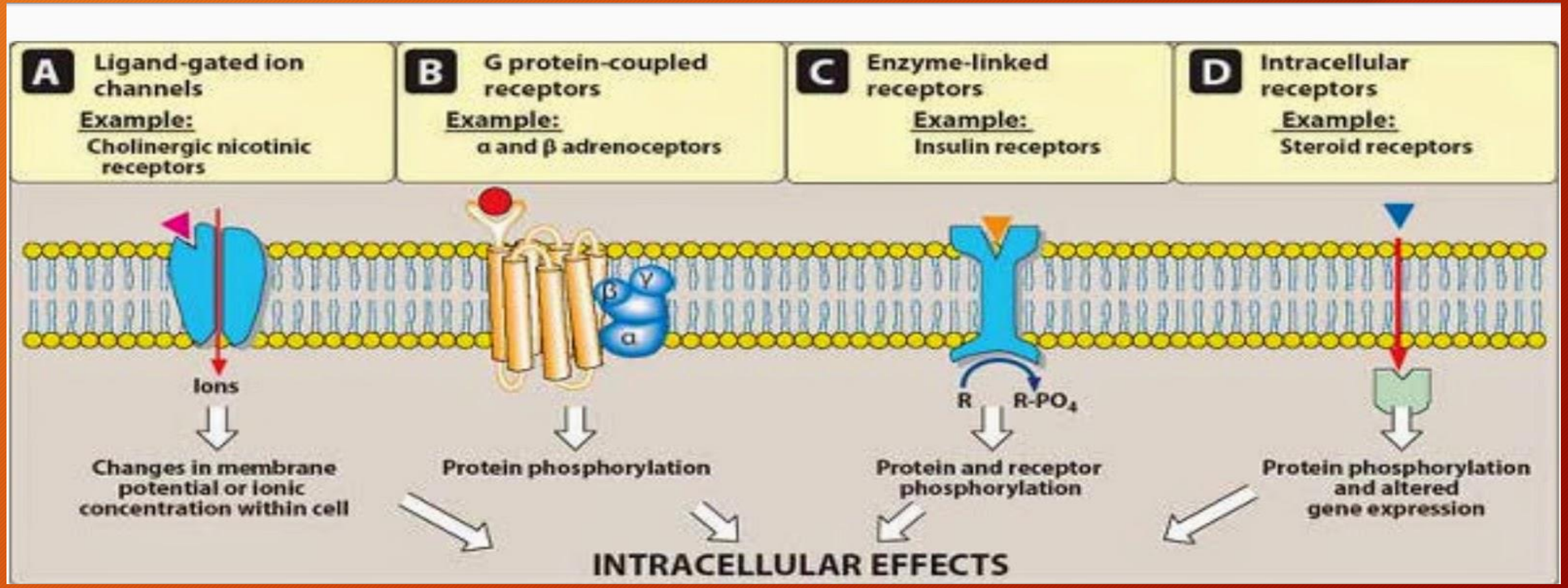
- The extracellular domain of this receptor contains the ligand-binding area
- The intracellular domain interacts (when activated) with a G protein or effector molecule.



b) Transmembrane G-Protein Coupled Receptors

- **Kinds of G proteins** (for example, Gs, Gi, and Gq), but they all are composed of <u>three protein subunits</u> (Alpha, beta and gamma)
- ***The a subunit binds*** guanosine triphosphate (GTP),
- **the β and γ subunits** anchor the G protein in the cell membrane (Figure)

G-Protein-Coupled receptors



b) Transmembrane G-Protein Coupled Receptors

- Binding of an agonist to the receptor → GTP binding to the α subunit→ causing dissociation of the α-GTP complex from the βγ complex.
- These two complexes can then interact with other cellular effectors - usually an enzyme, a protein, or an ion channel
- The effectors are responsible for further actions within the cell.
- These responses usually last several seconds to minutes

b) Transmembrane G-Protein Coupled Receptors and the concept of Second Messengers

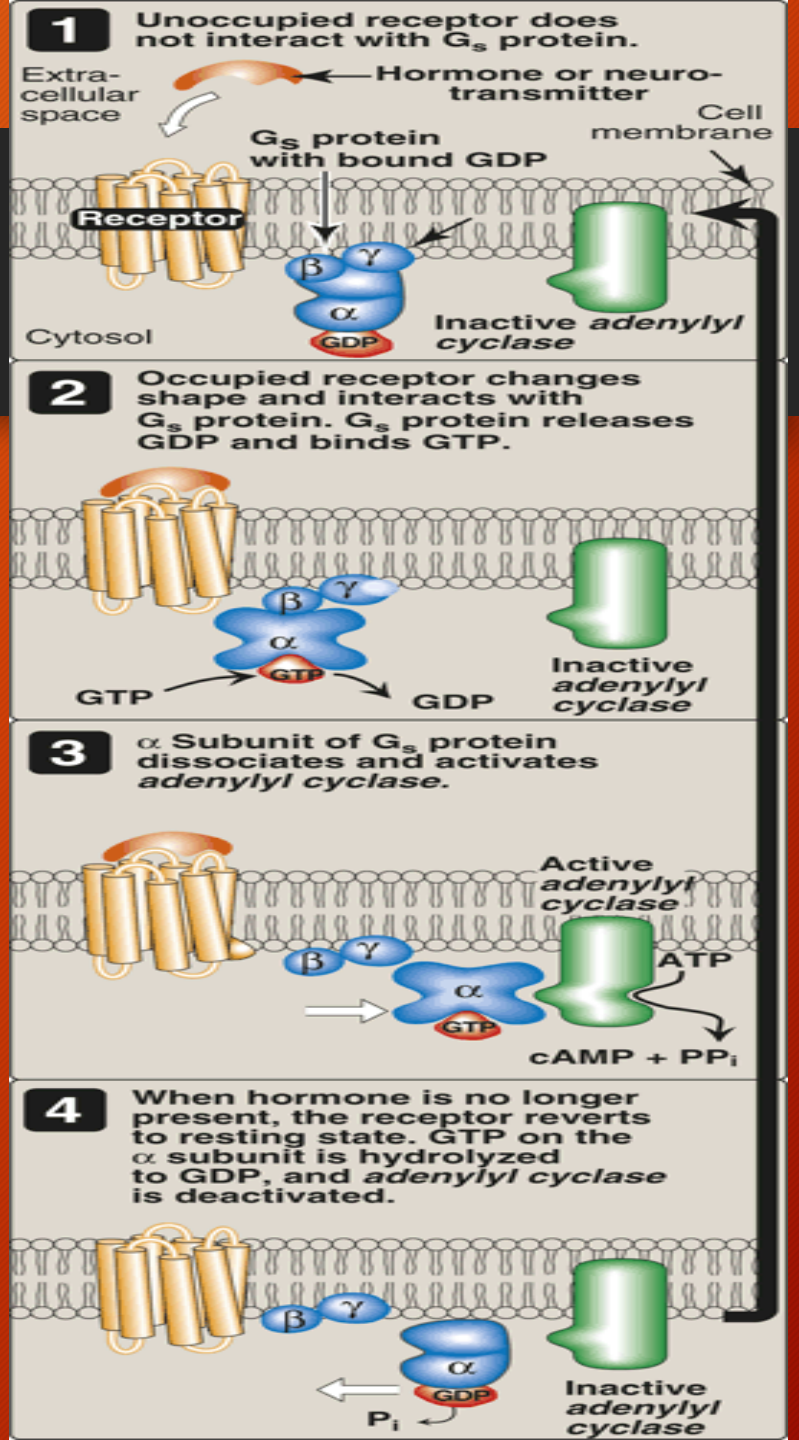
- Sometimes, the activated effectors produce second messengers that further activate other effectors in the cell, causing a signal cascade effect.
- A common effector, activated by Gs and inhibited by Gi, is adenylyl cyclase, which produces the second messenger cyclic adenosine monophosphate (cAMP).
- Gq activates phospholipase C, generating two other second messengers: inositol 1,4,5-trisphosphate (IP3) and diacylglycerol (DAG).

b) Transmembrane G-Protein Coupled Receptors and the concept of Second Messengers

- DAG and cAMP activate different→protein kinases within the cell, leading to → **a myriad of physiological effects.**

- IP3 regulates intracellular free calcium concentrations, as well as some protein kinases.

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



c) 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 (Figure)
- This response lasts on the order of minutes to hours.

c) Enzyme Linked Receptors

- 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 then other specific proteins (figure)

c) Enzyme Linked Receptors

- Phosphorylation can substantially modify the structure of the target protein, thereby acting as a molecular switch.

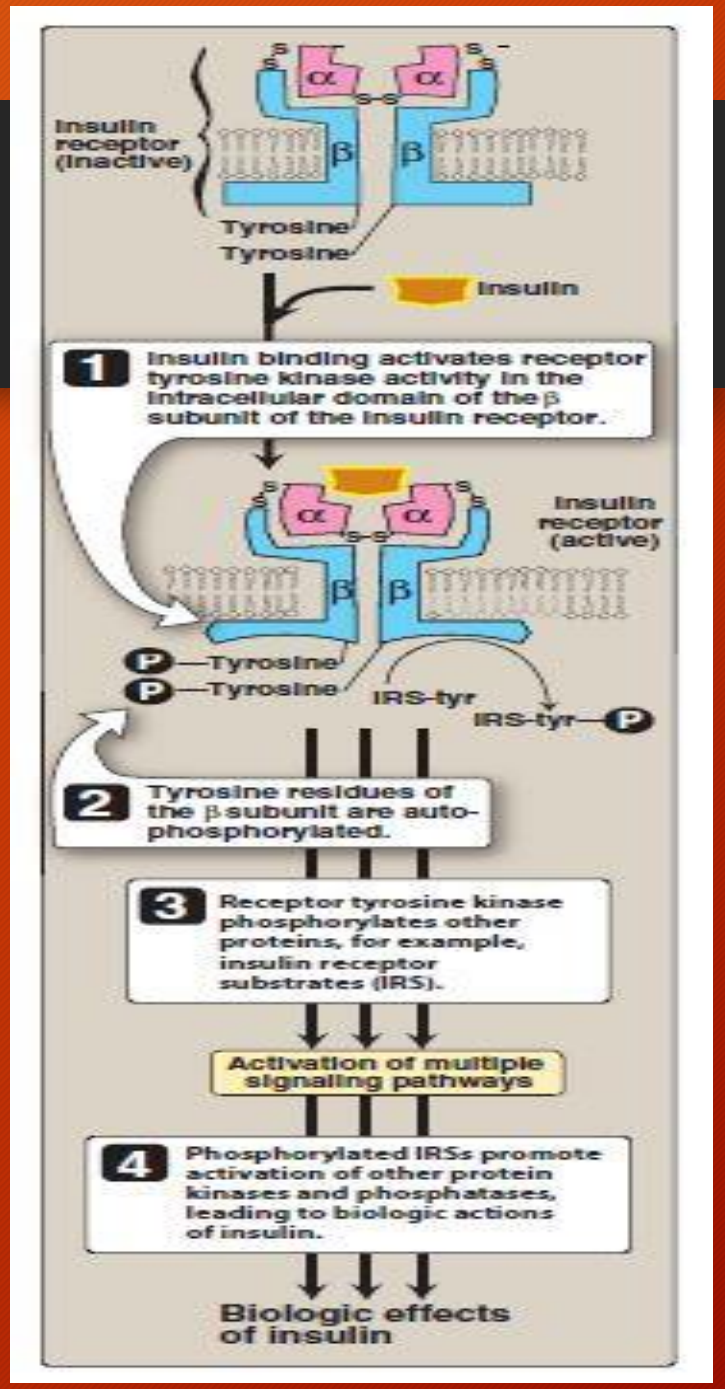
- E.g.when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself.

c) Enzyme Linked Receptors

- 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.

Enzyme Linked Receptors



d) Intracellular Receptors

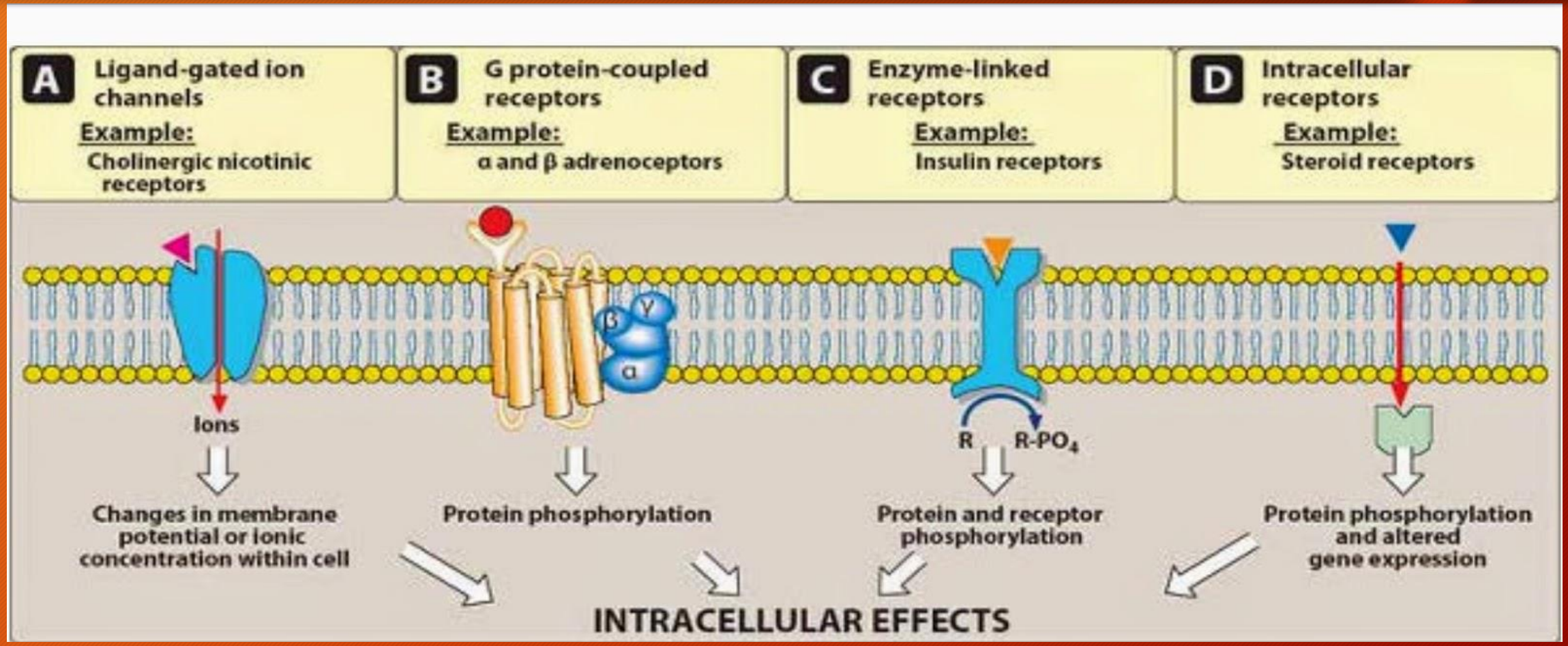
- Differs considerably from the other three
- The receptor is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor (Figure).
- In order to move across the target cell membrane, the ligand must have sufficient lipid solubility.
- The primary targets of these ligand–receptor complexes are transcription factors in the cell nucleus.

d) 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

Intracellular Receptors



d) Intracellular Receptors

- The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins.

- The time course of activation and response of these receptors is on the order of hours to days.

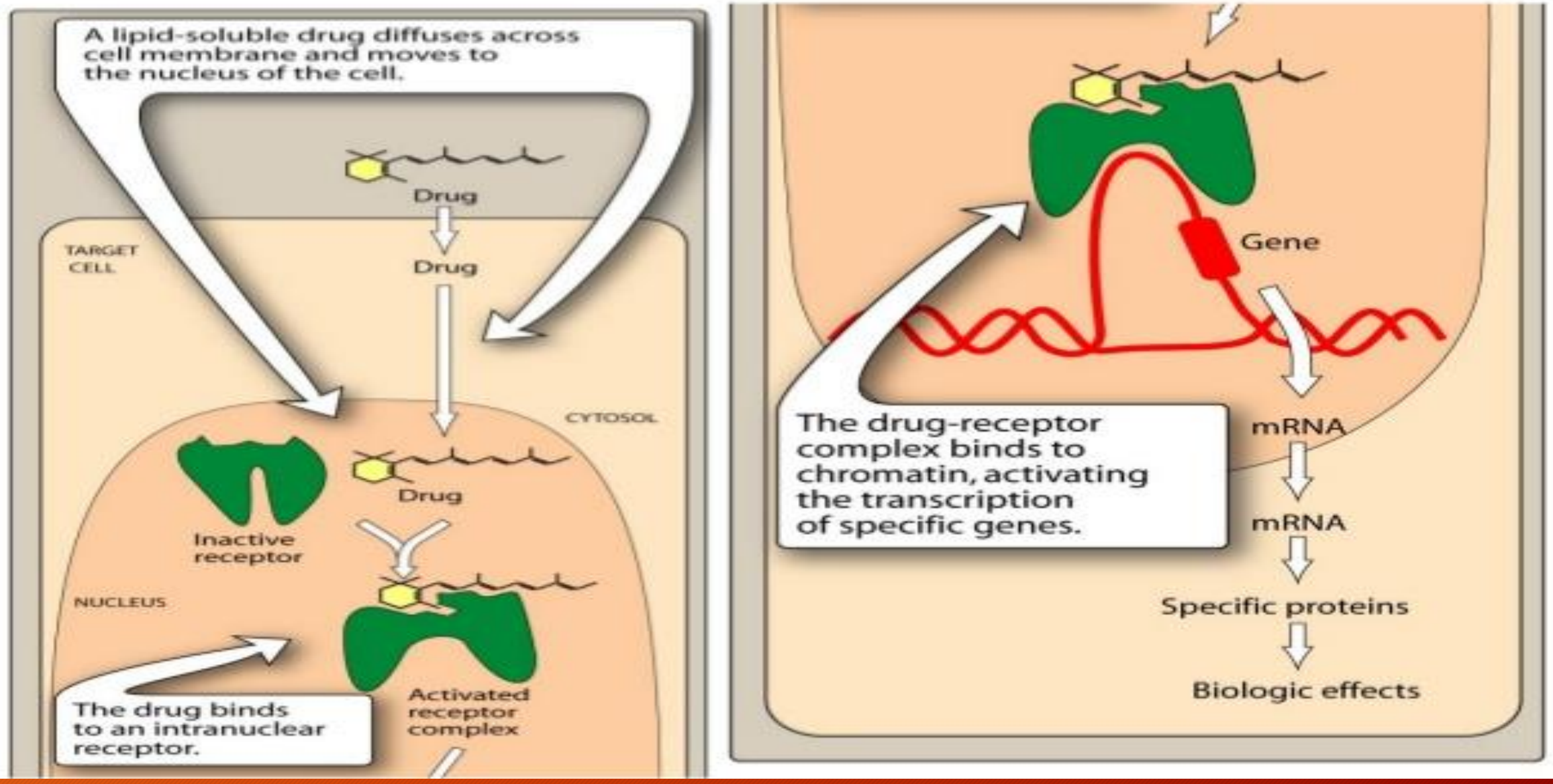
d) Intracellular Receptors

- E.g. Steroid hormones exert their action on target cells via intracellular receptors.
- Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes.

d) Intracellular Receptors

- 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*

Mechanism of intracellular receptors (e.g. nuclear receptors).



Regulation of Receptors

Upregulation of Receptors

- Repeated exposure to certain drugs causes increase in the number of receptors
- E.g. propranolol given over a long period of time causes increase in number of B-Receptors

Downregulation of Receptors

- Repeated exposure to certain drugs for prolonged period of time causes decrease in number of receptors for the drug

- E.g. levodopa given for more than 3-5 years can cause irreversible decrease in dopaminergic receptors by internalization and lysosomal degradation of receptors.

Desensitization of Receptors

- This is due to the repeated exposure to an agonist
- Like allergen which initially results in activation of receptors and later decreased response.
- On continuous exposure, activation of certain kinases and phosphorylation of receptor protein occurs.
- The receptor is internalized and finally degraded or recycled to the cell surface.

Thank You!!!