PRINCIPLES OF PHARMACODYNAMICS

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MECHANISMS OF DRUG ACTION

- **Drugs can act through:**

1. Physical action:

Drug can produce a therapeutic response because of it's physical properties. e.g**: Mannitol as diuretic** because it increase osmalerity, **Radio-isotopes** : emit ionizing radiation

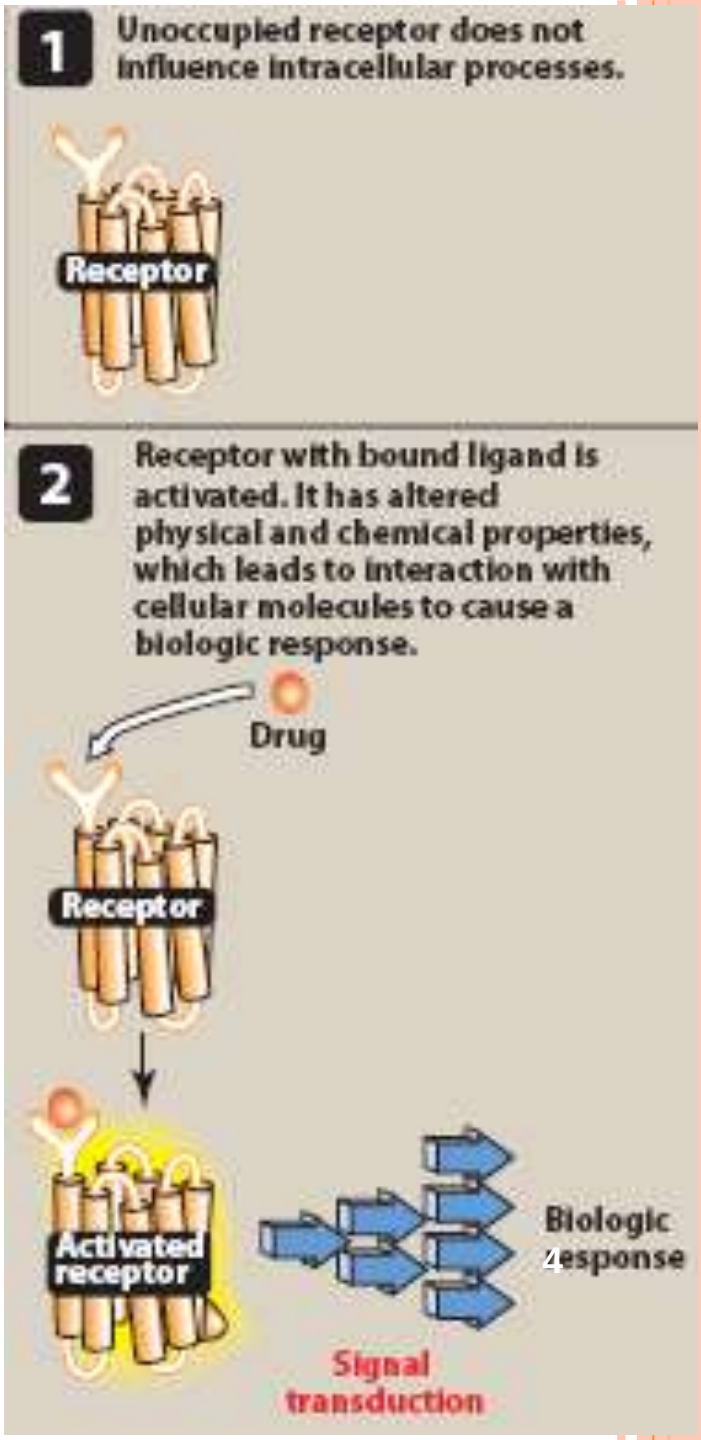
2. Simple chemical reaction:

Drug may act through a chemical reaction. e.g: **Gastric antacids** work by neutralizing the stomach acidity with a base, **Chelating agents** that bind heavy metals in body.

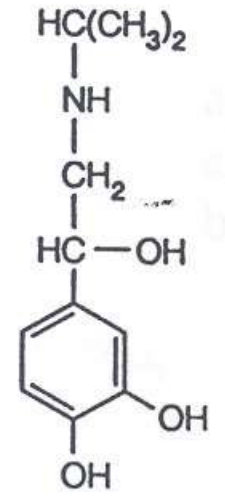
3. Receptors:

A receptor is a specialized target macromolecule mostly protein, present on the cell surface or intracellular, that binds a drug and mediates it's pharmacological actions.

- Receptors can either be enzymes, nucleic acids or structural proteins to which drugs may interact.
- A molecule that binds to a receptor is called a ligand, and can be a peptide or another small molecule like a neurotransmitter, hormone, or drug.
- Ligand binding changes the conformation (three-dimensional shape) of the receptor molecule. This alters the shape at a different part of the protein, changing the interaction of the receptor molecule with associated biochemicals, leading in turn to a cellular response mediated by the associated biochemical pathway.



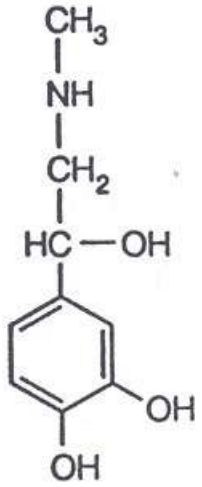
TYPES OF LIGAND-RECEPTOR INTERACTIONS



Isoproterenol

Agonist

e.g. important therapy in asthma

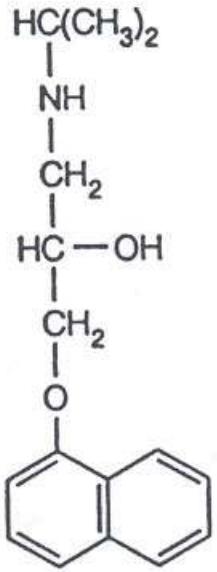


Epinephrine

Hormone

binds β_2 receptor in lung → bronchial relaxation

binds β_2 receptor in heart muscle → increased heart rate



Propranolol

Antagonist

control heart beat

TYPES OF LIGAND-RECEPTOR INTERACTIONS

Not every ligand that binds to a receptor also activates the receptor. The following classes of ligands exist:

1. **(Full) agonists** are able to activate the receptor and result in a maximal biological response. The natural endogenous ligand with greatest efficacy for a given receptor is by definition a full agonist (100% efficacy).
2. **Partial agonists** do not activate receptors thoroughly, causing responses which are partial compared to those of full agonists (efficacy between 0 and 100%).
3. **Antagonists** bind to receptors but do not activate them. This results in receptor blockage, inhibiting the binding of agonists and inverse agonists.
4. **Inverse agonists** reduce the activity of receptors by inhibiting their constitutive activity (negative efficacy).

Types of drug-receptor bonding

Drugs interact with receptors by means of chemical forces or bonds. These are of three major types:

1. Covalent: It is very strong and in many cases not reversible under biologic conditions. Thus, the duration of drug action is frequently, but not necessarily, prolonged (irreversible)

2. Electrostatic: is much more common than covalent bonding in drug-receptor interactions. These vary from relatively strong linkages between permanently charged ionic molecules to weaker hydrogen bonds and very weak induced dipole interactions such as van der Waals forces. Electrostatic bonds are weaker than covalent bonds. (reversible)

3. Hydrophobic: are usually quite weak and are probably important in the interactions of highly lipid-soluble drugs with the lipids of cell membranes and perhaps in the interaction of drugs with the internal walls of receptor "pockets.“

- Drugs which bind through weak bonds to their receptors are generally more selective than drugs which bind through very strong bonds.

- This is because weak bonds require a very precise fit of the drug to its receptor if an interaction is to occur

Duration of Drug Action

Termination of drug action at the receptor level results from one of several processes:

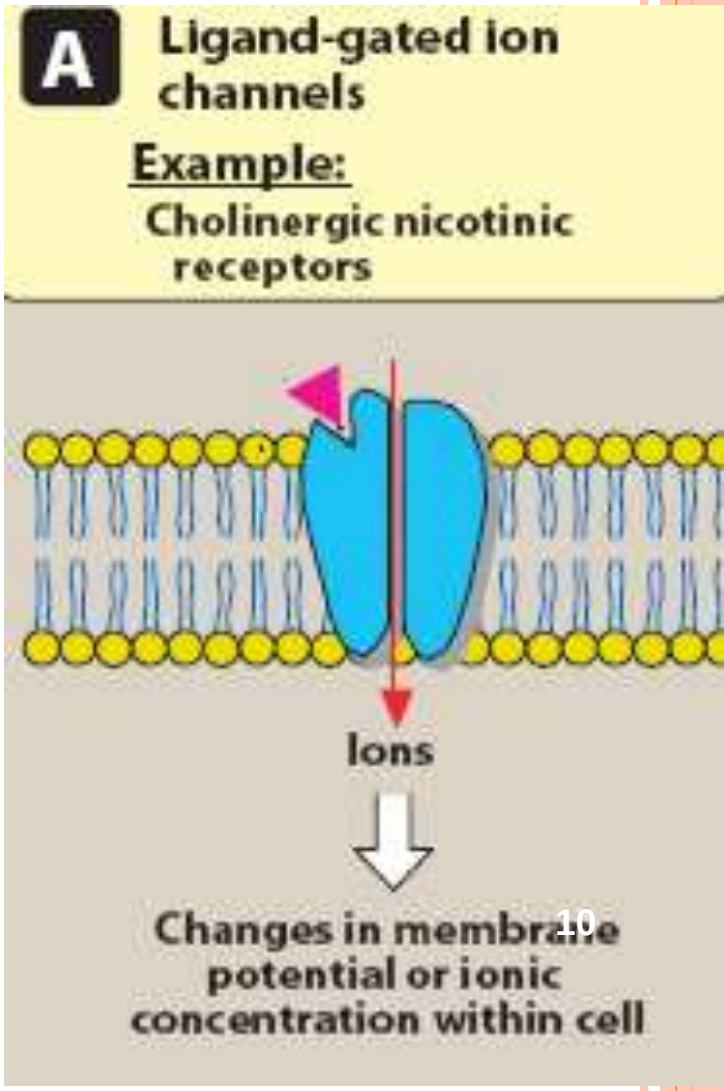
1. The effect lasts only as long as the drug occupies the receptor, so that dissociation of drug from the receptor automatically terminates the effect.
2. The action may persist after the drug has dissociated, because, for example, some coupling molecule is still present in activated form.
3. Drugs that bind covalently to the receptor, the effect may persist until the drug-receptor complex is destroyed and new receptors are synthesized.
4. Many receptor-effector systems incorporate desensitization mechanisms for preventing excessive activation when agonist molecules continue to be present for long periods

CLASSIFCATION OF RECEPTORS

This is based on the type of the transduction mechanism that these receptors activate when stimulated by their agonists:

1. Transmembrane ligand-gated ion channels: These receptors are present in the walls of ion channels in cell membranes. When activated by their specific agonist, they open these ion channels & lead to movement of ions across cell membrane.

➢These mediate diverse functions, including neurotransmission, cardiac conduction, and muscle contraction.



Examples :

1. **Nicotinic receptors** for acetylcholine (Ach.) : when stimulated, they open receptor-operated Na^+ channels, and thus increase influx of sodium ions across membranes of neurons or NMJ(neuromuscular junction) in skeletal muscle and therefore activation of contraction in muscle.

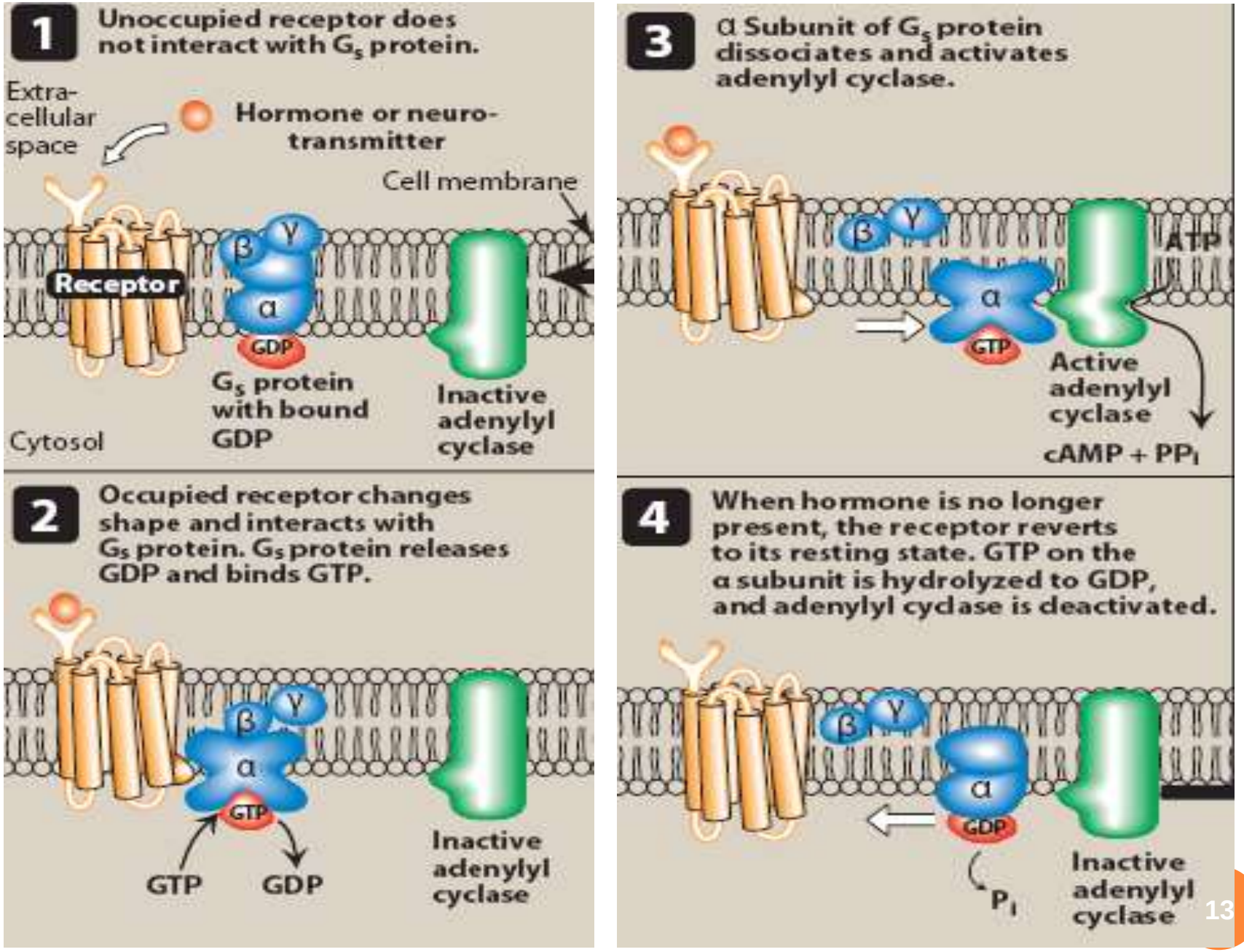
2. **γ-aminobutyric acid (GABA) receptors:**

   Benzodiazepines enhance the stimulation of the GABA receptor by GABA, resulting in increased chloride influx and hyperpolarization of the respective cell.

2. Transmembrane G protein–coupled receptors:

- When these receptors are stimulated by their specific agonists, they will activate a regulatory G-protein in cell membrane which in turn change activity of membrane enzymes (either adenyl cyclase or phospholipase C) leading to a change in intracellular level of a second messenger like cAMP (cyclic adenosine monophosphate), or IP_3 (inositol triphosphate), respectively, and this would lead to cell response.

- **Examples : e.g.** Receptors for transmitters : Stimulation of muscarinic receptors (M_1 and M_3) for Ach will activate G and leads to increase intracellular level of IP_3 & DAG



guanosine triphosphate (GTP), guanosine diphosphate (GDP)

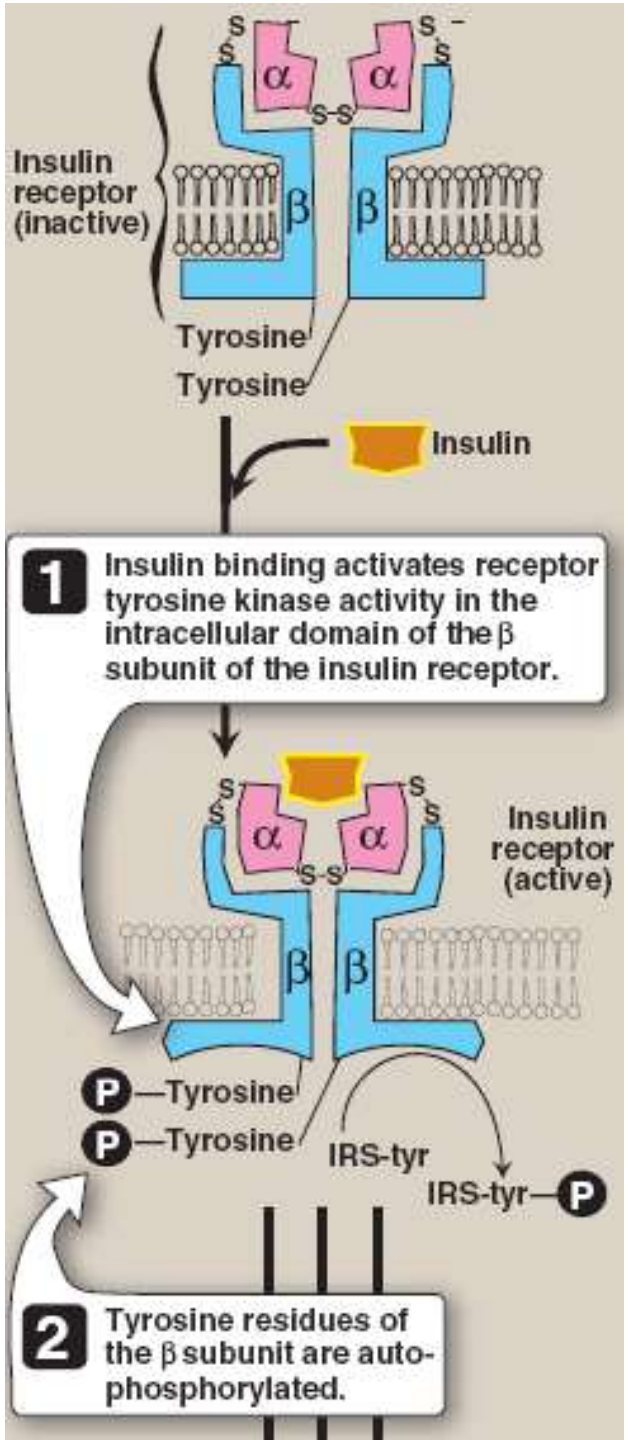
3. Enzyme-linked receptors:

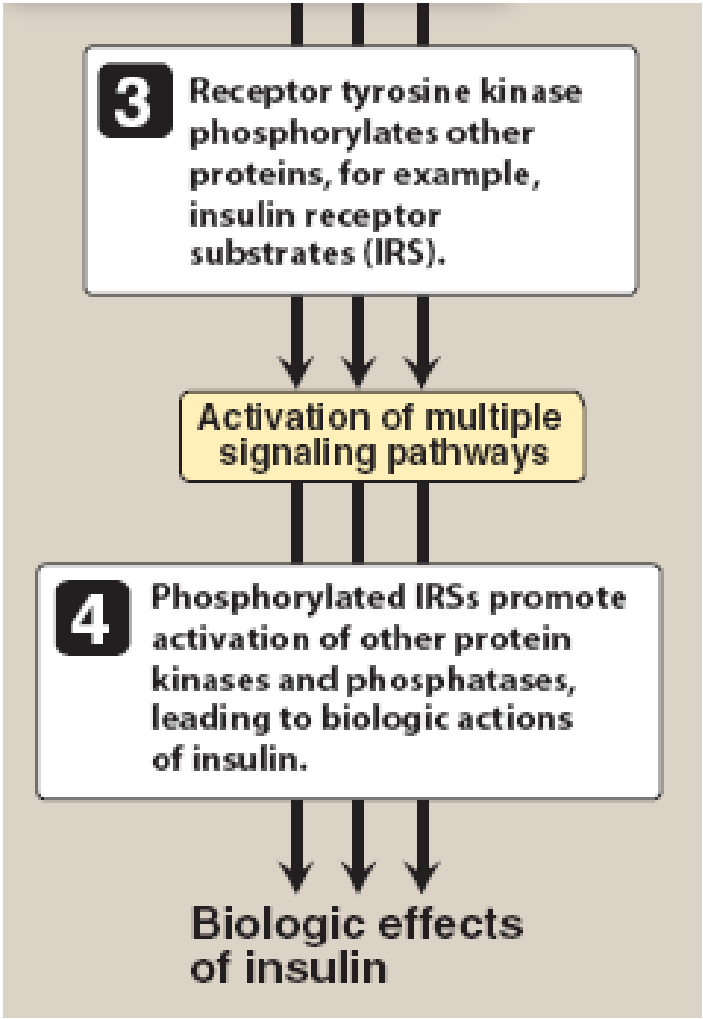
- These membrane receptors have an extra-cellular site that binds to specific agonists and an intra-cytoplasmic domain which contains tyrosine and other amino acids.

- **Binding to specific agonist and activation of these receptors usually lead to phosphorylation of tyrosine in intra-cellular domain** which then **acquires kinase activity** and leads to activation of intracellular substrates or enzymes that finally leads to cell response.

- **Examples:**

  Receptors for insulin,
  Receptors for growth factors like EGF or PDGF,
  Receptors for immune cytokines

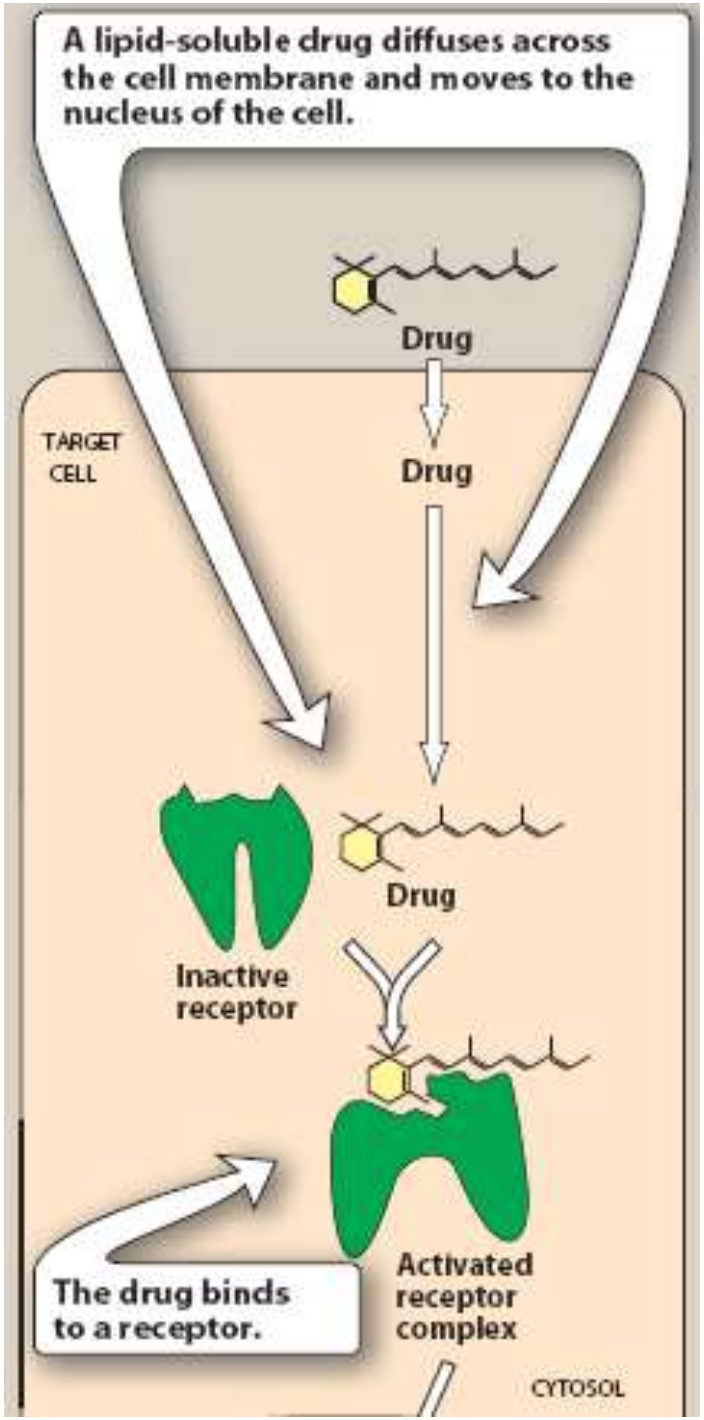

Insulin receptor (inactive)
α
α
β
β
Tyrosine
Tyrosine
Insulin
1 Insulin binding activates receptor tyrosine kinase activity in the intracellular domain of the β subunit of the insulin receptor.
Insulin receptor (active)
P—Tyrosine
P—Tyrosine
IRS-tyr
IRS-tyr—P
2 Tyrosine residues of the β subunit are auto-phosphorylated.

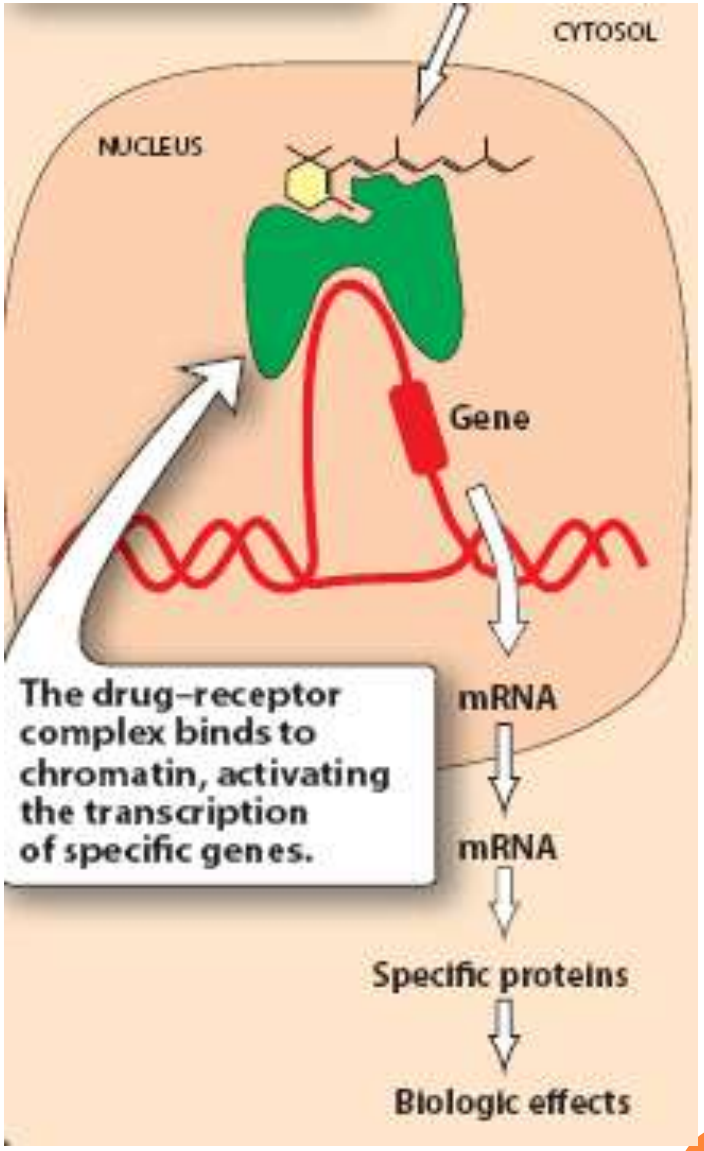

3 Receptor tyrosine kinase phosphorylates other proteins, for example, insulin receptor substrates (IRS).
Activation of multiple signaling pathways
4 Phosphorylated IRSs promote activation of other protein kinases and phosphatases, leading to biologic actions of insulin.
Biologic effects of insulin

4. Intracellular receptors:

- These receptors are **located in cytoplasm** (e.g. steroid receptors) or **nucleus** (receptors for thyroid hormones or vitamin D_3) .

- The specific agonist must cross cell membrane to inside of cell, binds and activates these receptors, which will then bind to DNA gene response elements in nucleus and lead to change in gene transcription , and thus synthesis of new proteins


A lipid-soluble drug diffuses across the cell membrane and moves to the nucleus of the cell.
Drug
TARGET CELL
Drug
Drug
Inactive receptor
The drug binds to a receptor.
Activated receptor complex
CYTOSOL


CYTOSOL
NUCLEUS
Gene
The drug–receptor complex binds to chromatin, activating the transcription of specific genes.
mRNA
mRNA
Specific proteins
Biologic effects

THANKS