Receptors Families

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Receptor Families

1. Ligand-gated ion channels
2. G protein–coupled receptors
3. Enzyme-linked receptors
4. Intracellular receptors

Ligand-gated ion channels

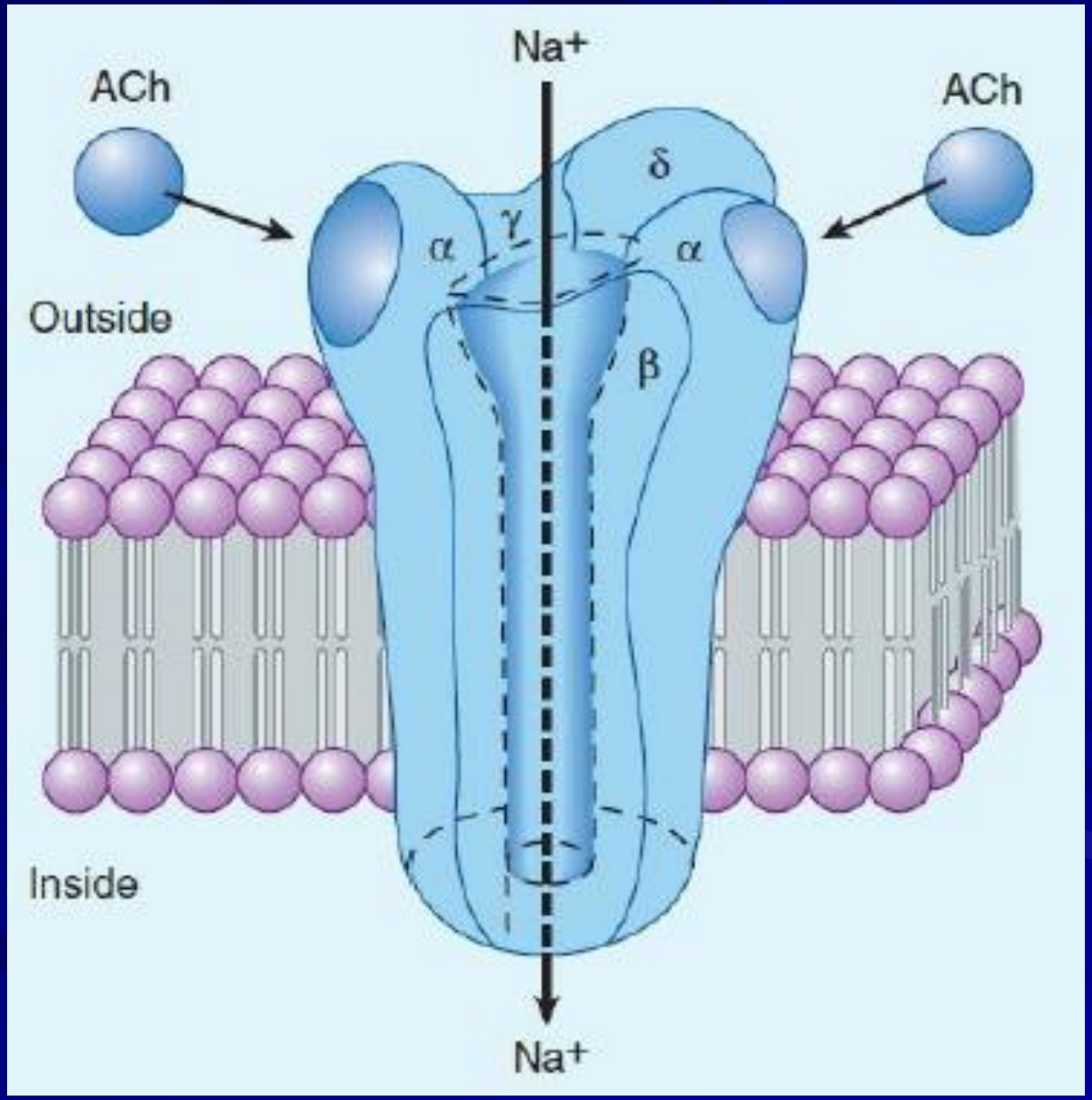
Many of the most useful drugs in clinical medicine act by mimicking or blocking the actions of endogenous ligands that regulate the flow of ions through plasma membrane channels.

The natural ligands of such receptors include acetylcholine, serotonin, GABA, and glutamate (All of these agents are synaptic transmitters)

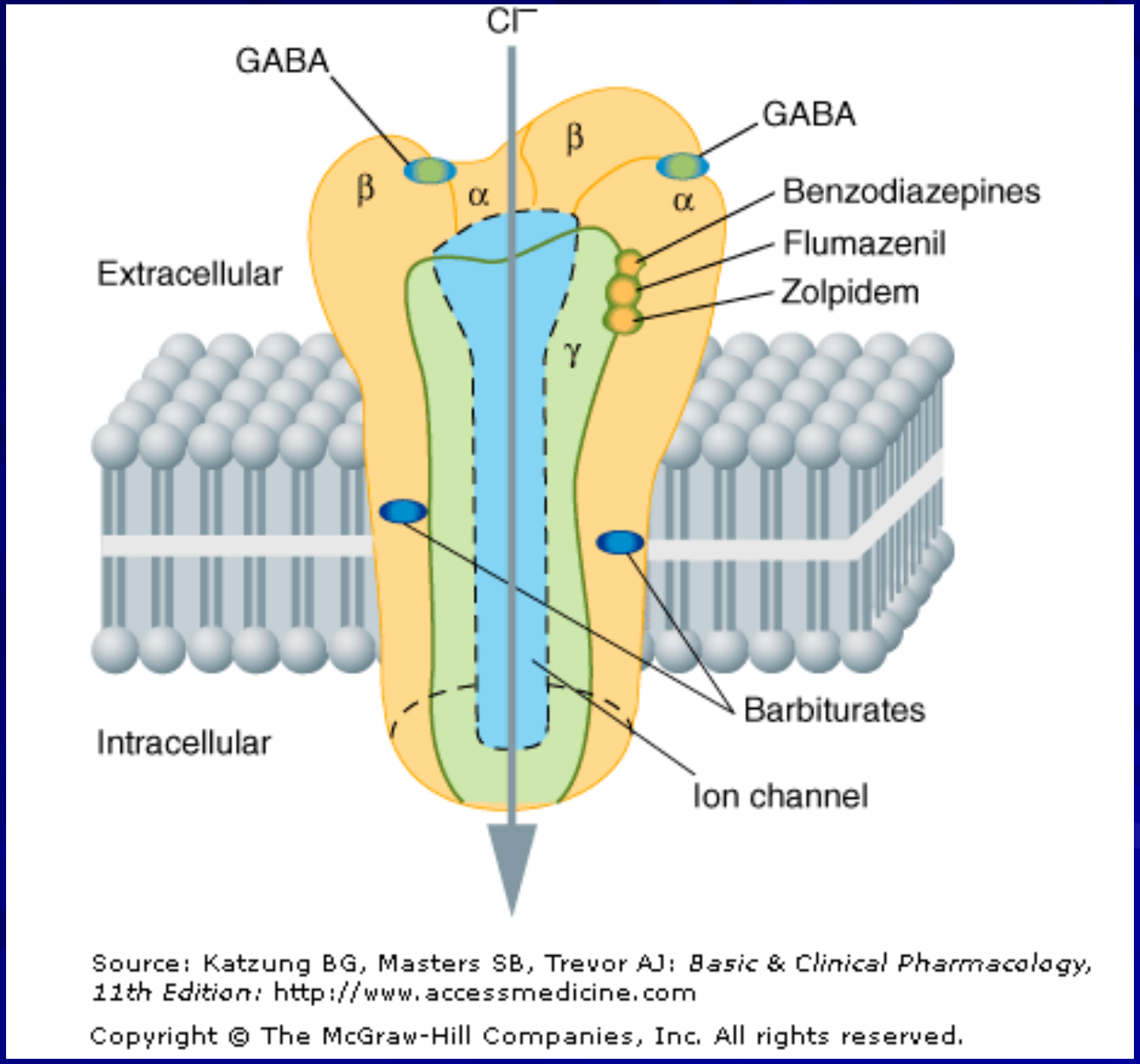
- Responsible for regulation of the flow of ions across cell membranes
- The activity of these channels is regulated by the binding of a ligand to the channel
- Response to these receptors is very rapid, measured in milliseconds
- The rapidity of this signaling mechanism is important for moment-to-moment transfer of information across synapses
- The nicotinic receptor and the γ-aminobutyric acid (GABA) receptor are important examples of ligand-gated receptors.

- The nicotinic acetylcholine (ACh) receptor, a ligand-gated ion channel. The receptor molecule is embedded in plasma membrane, with extracellular fluid above and cytoplasm below. Composed of five subunits (two α, one β, one γ, and one δ), the receptor opens a central transmembrane ion channel when ACh binds to sites on the extracellular domain of its α subunits

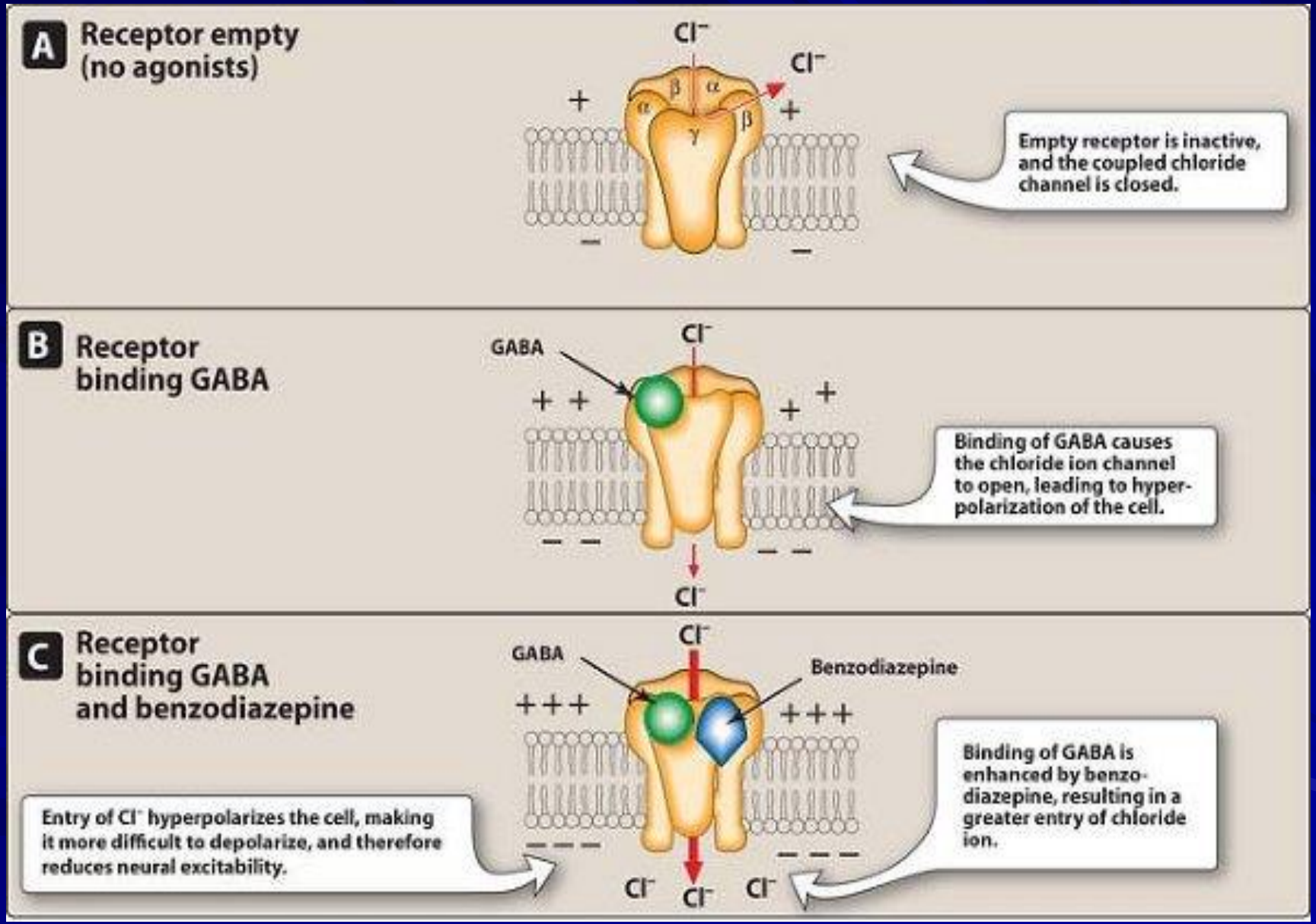
- Stimulation of the nicotinic receptor by acetylcholine results in sodium influx, generation of an action potential and activation of contraction in skeletal muscle.


Na+
ACh
ACh
δ
γ
α
α
Outside
β
Inside
Na+

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



Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition:* http://www.accessmedicine.com


A
Receptor empty (no agonists)
Cl⁻
Cl⁻
β
α
α
β
γ
+
+
−
−
Empty receptor is inactive, and the coupled chloride channel is closed.
B
Receptor binding GABA
GABA
Cl⁻
+ +
+ +
− −
− −
Binding of GABA causes the chloride ion channel to open, leading to hyper-polarization of the cell.
Cl⁻
C
Receptor binding GABA and benzodiazepine
GABA
Cl⁻
Benzodiazepine
+++
+++
− − −
− − −
Entry of Cl⁻ hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability.
Binding of GABA is enhanced by benzo-diazepine, resulting in a greater entry of chloride ion.
Cl⁻
Cl⁻
Cl⁻

- verapamil inhibits voltage-gated calcium channels that are present in the heart and in vascular smooth muscle, producing antiarrhythmic effects and reducing blood pressure without mimicking or antagonizing any endogenous transmitter

G-protein-coupled Receptors (GPCRs)

- GPCRs transduces signals derived from neurotransmitters, including norepinephrine, dopamine, serotonin and acetylcholine
- These receptors are a single peptide that has seven membrane-spanning regions
- Stimulation of these receptors results in responses that last several seconds to minutes

G Protein–coupled Receptors

- Binding of the 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 release of activated Gα and Gβγ units
- These activated units modulate cytoplasmic effectors.

  usually an enzyme or ion channel.
- The effectors synthesize or release second messengers such as cAMP, IP3, and DAG, that are responsible for further actions within the cell.

Second Messengers

These are essential in conducting and amplifying signals coming from G protein-coupled receptors.

Cyclic Adenosine Monophosphate (cAMP)

- The production of cAMP result from activation of adenylyl cyclase(effector) by α-GTP subunits
- cAMP regulates protein phosphorylation.

Inositol-trisphosphate (IP_3) & Diacylglycerol DAG

- G proteins activate phospholipase C (effector), & the generation of these second messengers occur
- These effectors are responsible for the regulation of intracellular free calcium concentrations and of other proteins

Cyclic Guanosine Monophosphate (cGMP)

- The production of cGMP result from activation of guanylyl cyclase (effector) by α-GTP subunits then this effector converts GTP to cGMP.
- cGMP stimulates cGMP-dependent protein kinase.
- cGMP signaling is important in only a few cells, for example, intestinal mucosa and vascular smooth muscle, where it causes relaxation of vascular smooth muscle cells.

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

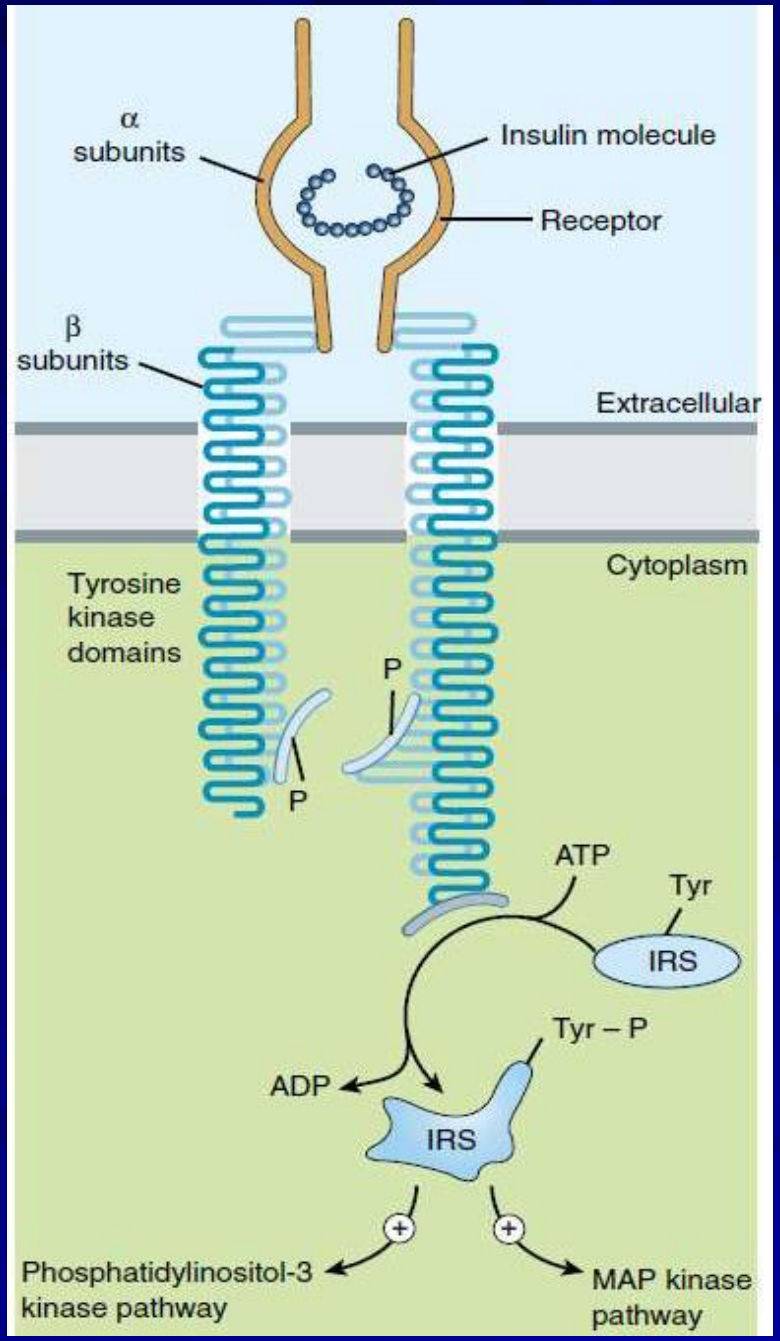
Enzyme-linked Receptors

- Those having cytosolic enzyme activity
- Binding of a ligand to an extracellular domain activates or inhibits this 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 and others) are those that have a tyrosine kinase activity as part of their structure.
- 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.

Example: Insulin Receptor

- Two α subunit (extracellular) and two β subunit (trans membrane)
- The β subunit contains a tyrosine kinase.
- The binding of an insulin molecule to the α subunits at the outside surface of the cell activates the receptor and lead to conformational change of the opposing cytoplasmic β subunits , this facilitates phosphorylation of tyrosine residues on the β subunits, and activation of a variety of intracellular proteins.


α
subunits
Insulin molecule
Receptor
β
subunits
Extracellular
Cytoplasm
Tyrosine
kinase
domains
P
P
ATP
Tyr
IRS
Tyr – P
ADP
IRS
+
+
Phosphatidylinositol-3
kinase pathway
MAP kinase
pathway

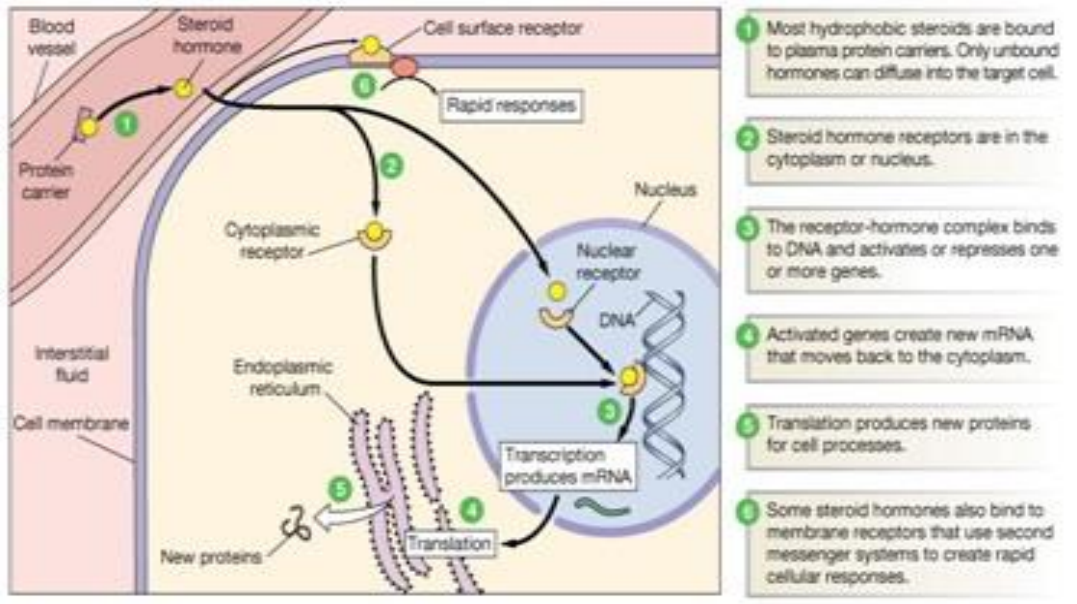
Intracellular Receptors

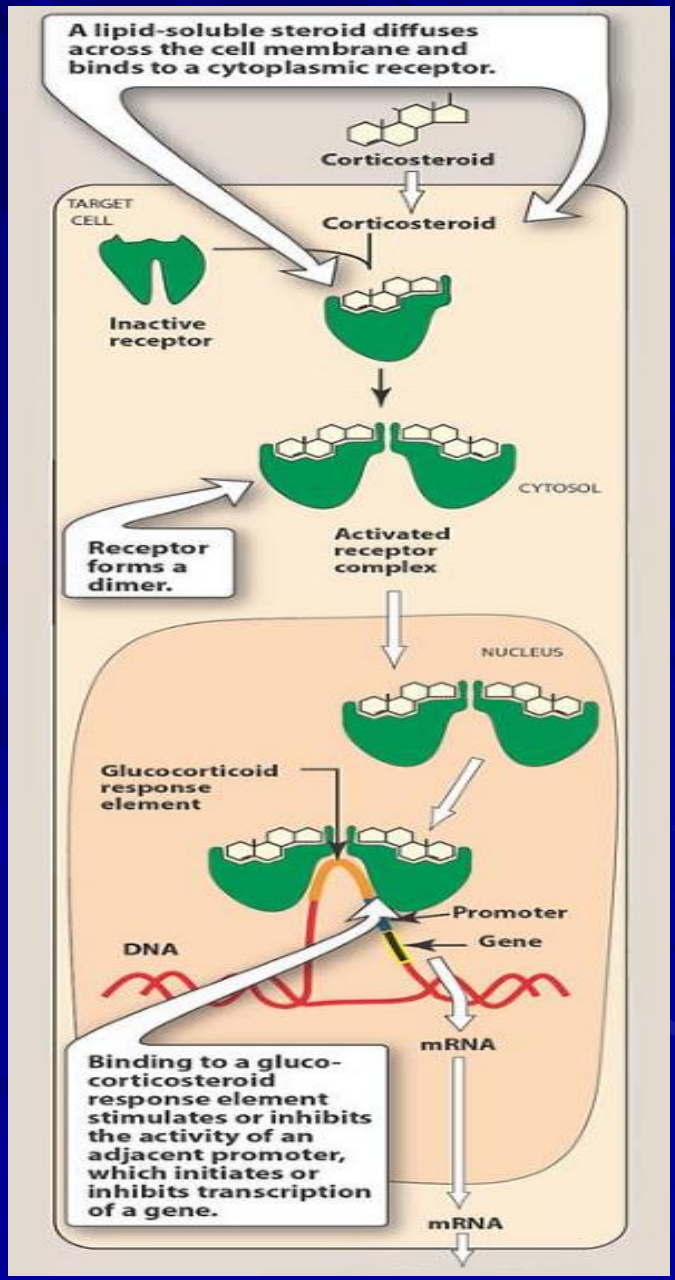
- The receptor is intracellular, the ligand must diffuse into the cell to interact with the receptor.
- The physical and chemical properties of the ligand in that it must have sufficient lipid solubility to be able to move across the target cell membrane. Because these receptor ligands are lipid soluble, they are transported in the body attached to plasma proteins, such as albumin.

For Example, Steroid Hormones

- Only unbound hormones can diffuse into the target cell.
- They bind to specific intracellular receptors in target tissues.
- The receptor-hormone complex binds to DNA and activates or represses one or more genes.
- Activated genes create new mRNA that move back to cytoplasm.
- Translation produces new proteins for cell processes

Steroid Hormones





- 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.