HORMONES ACTION/SIGNAL TRANSDUCTION

Biochemistry

Biomedical Importance

- Intercellular communication mechanisms are necessary requirements for this adaptation.

- The nervous system and the endocrine system provide this intercellular, organism-wide communication.

- neural regulation of the endocrine system is important in the production and secretion of some hormones

- many neurotransmitters resemble hormones in their synthesis, transport, and mechanism of action; and many hormones are synthesized in the nervous system.

- A hormone–receptor interaction results in generation of an intracellular signal that can either **regulate the activity of a select set of genes,** thereby altering the amount of certain proteins in the target cell,
- or **affect the activity of specific proteins**, including enzymes and transporter or channel proteins.

- The signal can influence the location of proteins in the cell and **can affect general processes** such as **protein synthesis, cell growth, and replication**, perhaps through effects on gene expression.

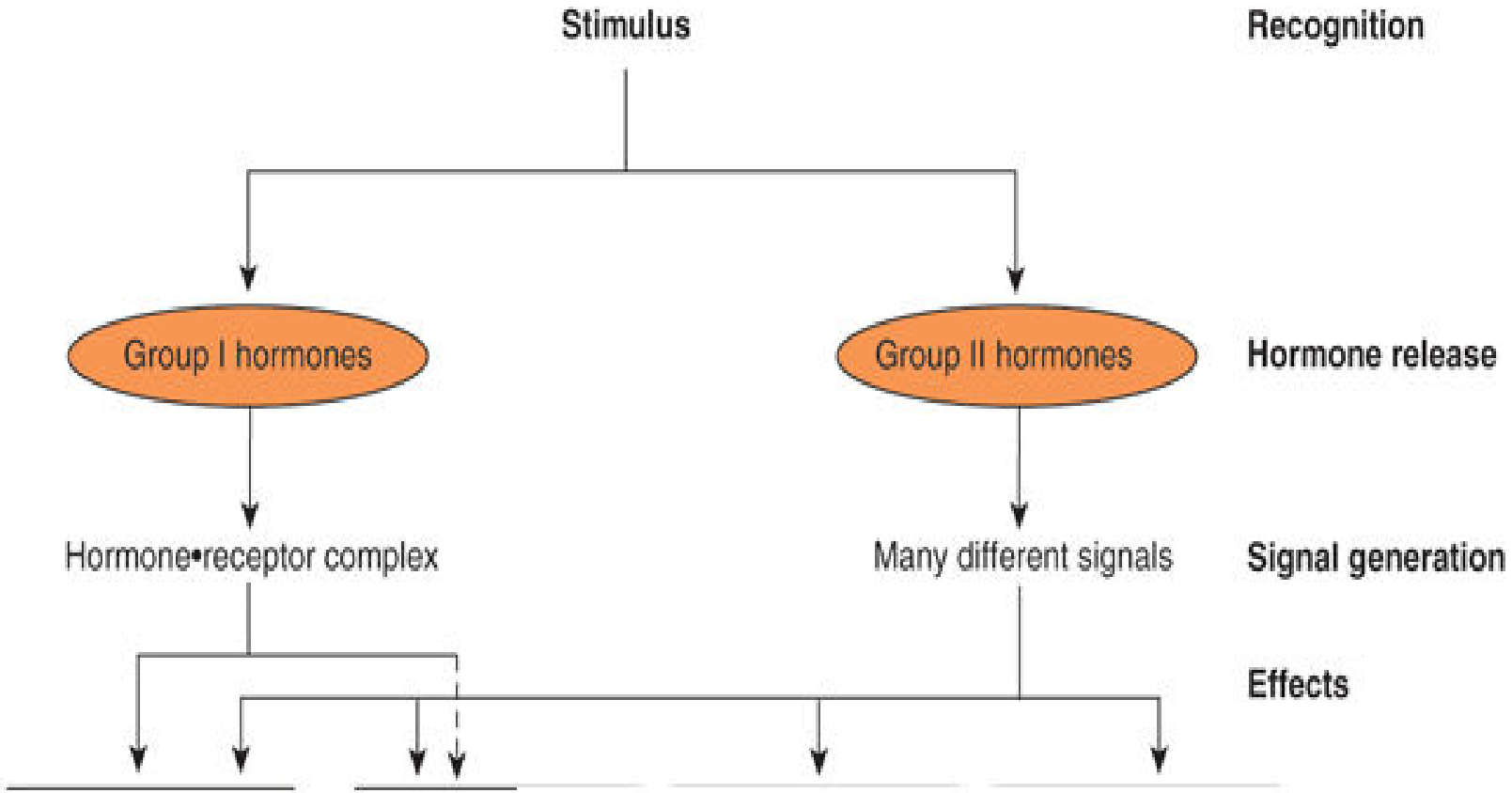
coordinated response to a particular stimulus

- The stimulus can be a challenge or a threat to the organism, to an organ, or to the integrity of a single cell within that organism.

- Recognition of the stimulus is the first step in the adaptive response.

- At the **organismic level**, this generally involves the **nervous system and the special senses (sight, hearing, pain, smell, touch).**

- At the **cellular level**, recognition involves physicochemical factors such as **pH, O_2 tension, temperature, nutrient supply, noxious metabolites, and osmolarity**

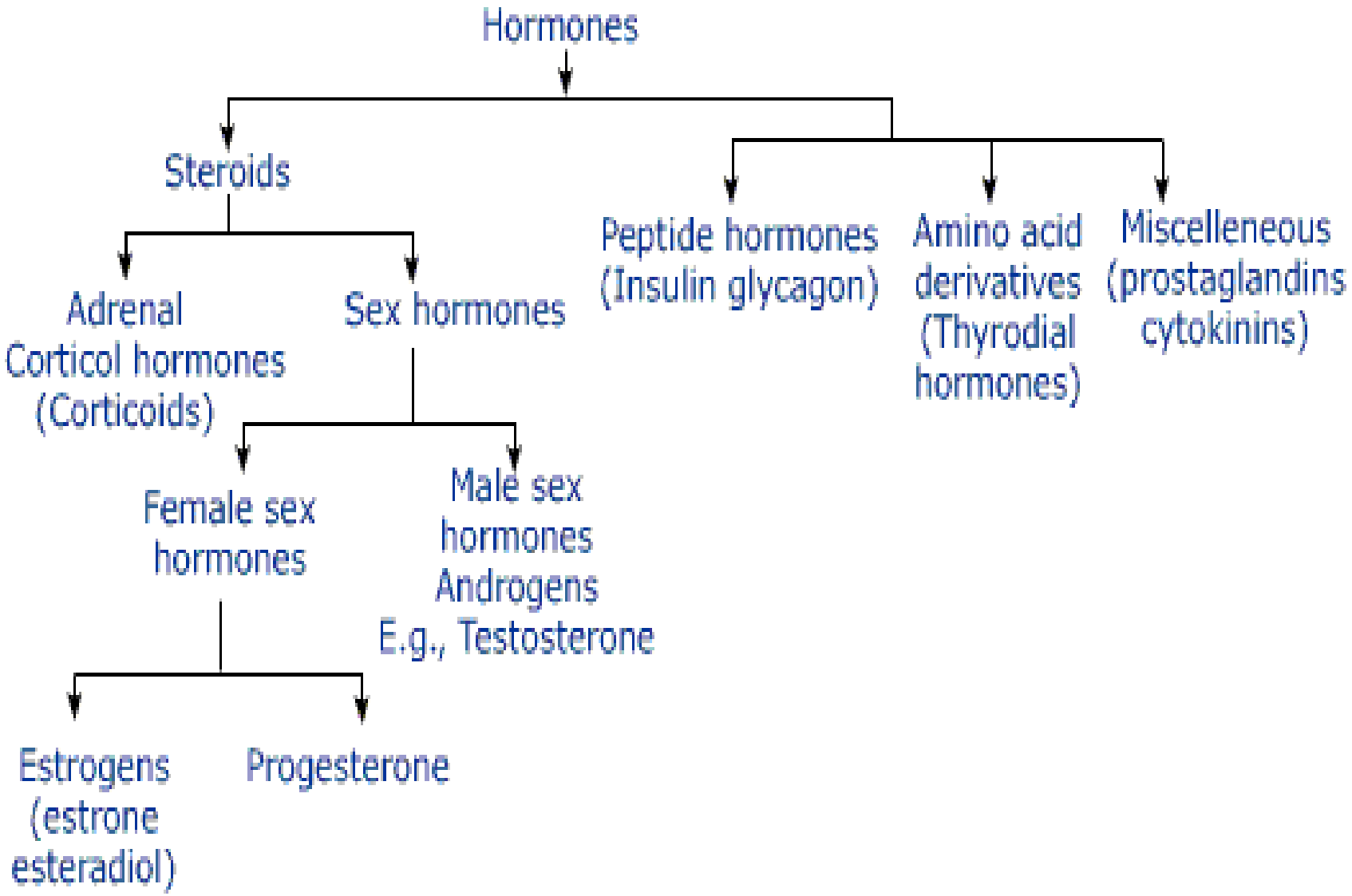


Classification of Hormones

- Hormones are classified on the basis of:

(i) Their structure.

(ii) Their site of activity in the cell.



General features of Hormone classes

GROUP –I

Types- steroids hormones

Solubility – Lipophilic

Transport Proteins- Yes

Plasma half life- long

Receptor- Intracellular

Mediator- Receptor- Hormone complex

GROUP –II

Types- Polypeptides, proteins, glycoproteins, catecholamine hormones

Solubility – Hydrophilic

Transport Proteins- No

Plasma half life- Short

Receptor- Plasma membrane

Mediator- cAMP, cGMP, Calcium and phosphatidylinostinol.

Transduction:

The biochemical mechanism(s) that allow the transfer of information between an occupied hormone-receptor & the molecules within the cell that result in production of a cellular response.

Ligand
Receptor
Transducer
Effector

} **Amplifiers**

Change in metabolism
Change in transcription/gene-read out
Change in secondary hormone production

RECEPTORS

- These are proteins, to which hormones bind. **They are present in cell membranes, cytoplasm and nucleus, and serve two functions**.
- Firstly, they are required for **selectivity.** Secondly, they are connected to an **effecter mechanism** in the cell .

- Selectivity

- Effecter mechanism- receptor has got two domains.

1. Binding domain
2. Signal generation domain

Transduction System Concepts

Features of transduction that both **alter protein shape & function**

Allosteric changes
Phosphorylation

Membrane Receptors

usually for proteins & charged molecules
rapid response systems, sec-min

Intranuclear Receptors

lipids & hydrophobic hormones
longer term responses, min-days

Transduction Pathways Depend on Receptor Types

- **Ion Channels**
- **Intracellular/Intranuclear Receptor**
  - Steroids (sex, adrenal, vitamin D, sterols)
  - Thyronines (tri-iodothyronine)
- **G-Protein Receptors/Serpentine Receptors**
  - cGMP/NOS
  - cAMP/PKA/CREB
  - PLCβ/PKC/Calcium ion
- **Cytokine & GH Receptors**
  - JAK/STAT
  - TyrK
    - Ras/GAP/MEK/MAPK
    - RAC/Rho
    - PI3K
    - PLCγ/PKC

Cross-talk allows unique responses in specific tissues & /or at specific times.

- Translate information in hormone messages into language that can be interpreted & acted upon by target cells.

- For proteins, peptides, & hormones with a high ionic charge at neutral pH, receptors are usually integral membrane proteins in the cell surface. When hormones bind, **the receptors interact with membrane-bound or intracellular transducer proteins to begin the cascade of events leading to cellular response**

- Some membrane receptors, *e.g.*, the acetyl-choline receptor, act as ion channels that open or close in response to hormone binding & induce changes via changes of the intracellular ion/charge balance.

- For many lipophilic hormones, *e.g.*, steroids or thyronines, receptors are intracellular, usually intranuclear, proteins.
- When their specific *ligands* bind, the hormone-receptor complexes undergo conformational changes that allow them to interact with specific hormone recognition sites (HREs) in the DNA of the regulatory regions of certain genes

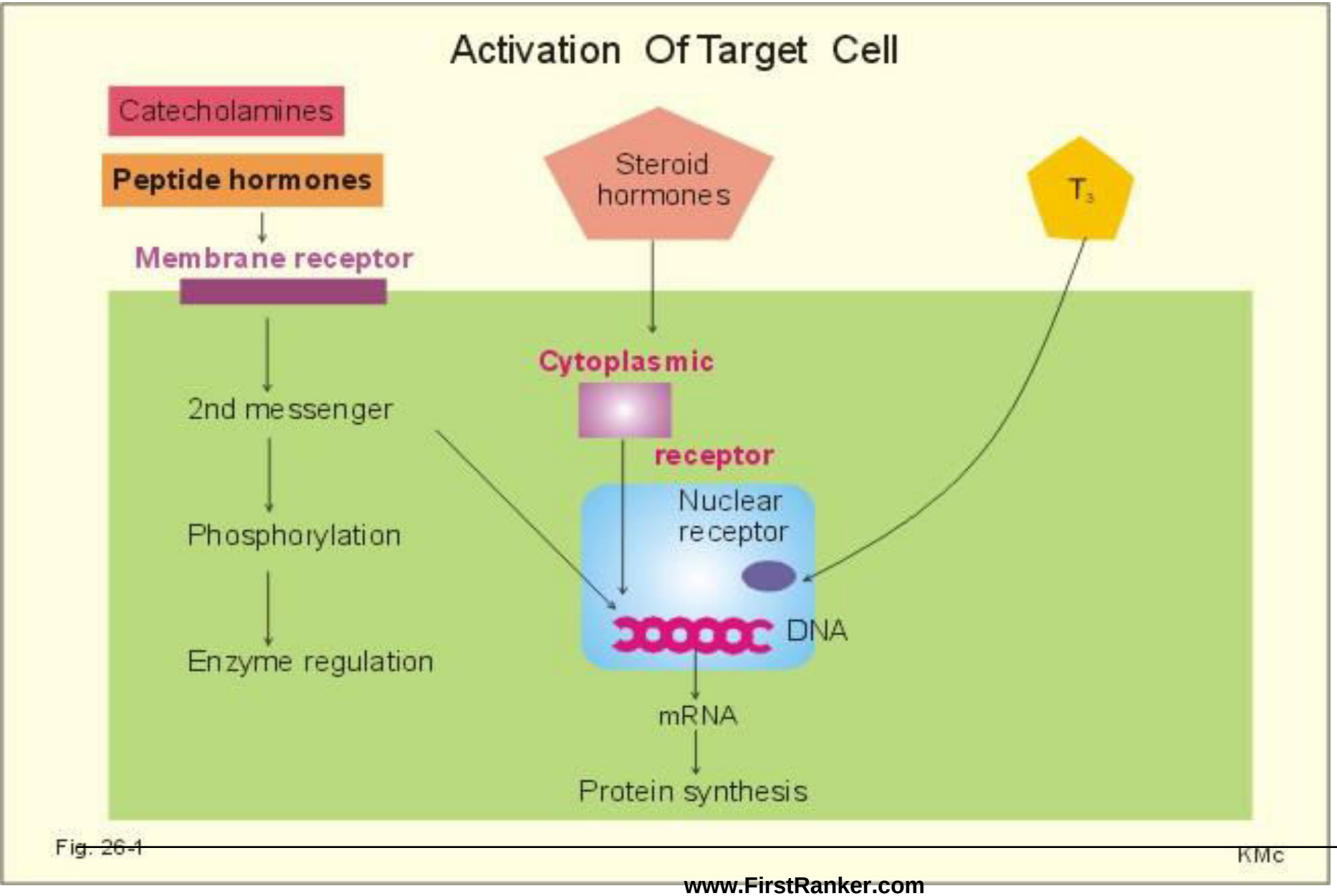


Fig. 26-1

KMc

Domains present on the receptors

- All receptors have two functional domains:

1. Recognition domain
2. Coupling domain.

- Recognition domain: it binds the hormone
- Coupling domain: it generates a signal that couples the hormone recognition to some intracellular function.
- Coupling means signal transduction.
- Receptors are proteins.

(Steroid, Retinoid and Thyroid have several functional domains):

- Binding of ligand
- Binding of DNA
- Binding of co regulator proteins(activation or inhibition)
- Binding of other proteins that specify intracellular trafficking of receptor.

RECEPTORS

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- Firstly, they are required for selectivity. Secondly, they are connected to an effecter mechanism in the cell .

- Selectivity

- Effecter mechanism- receptor has got two domains.

1. Binding domain
2. Signal generation domain

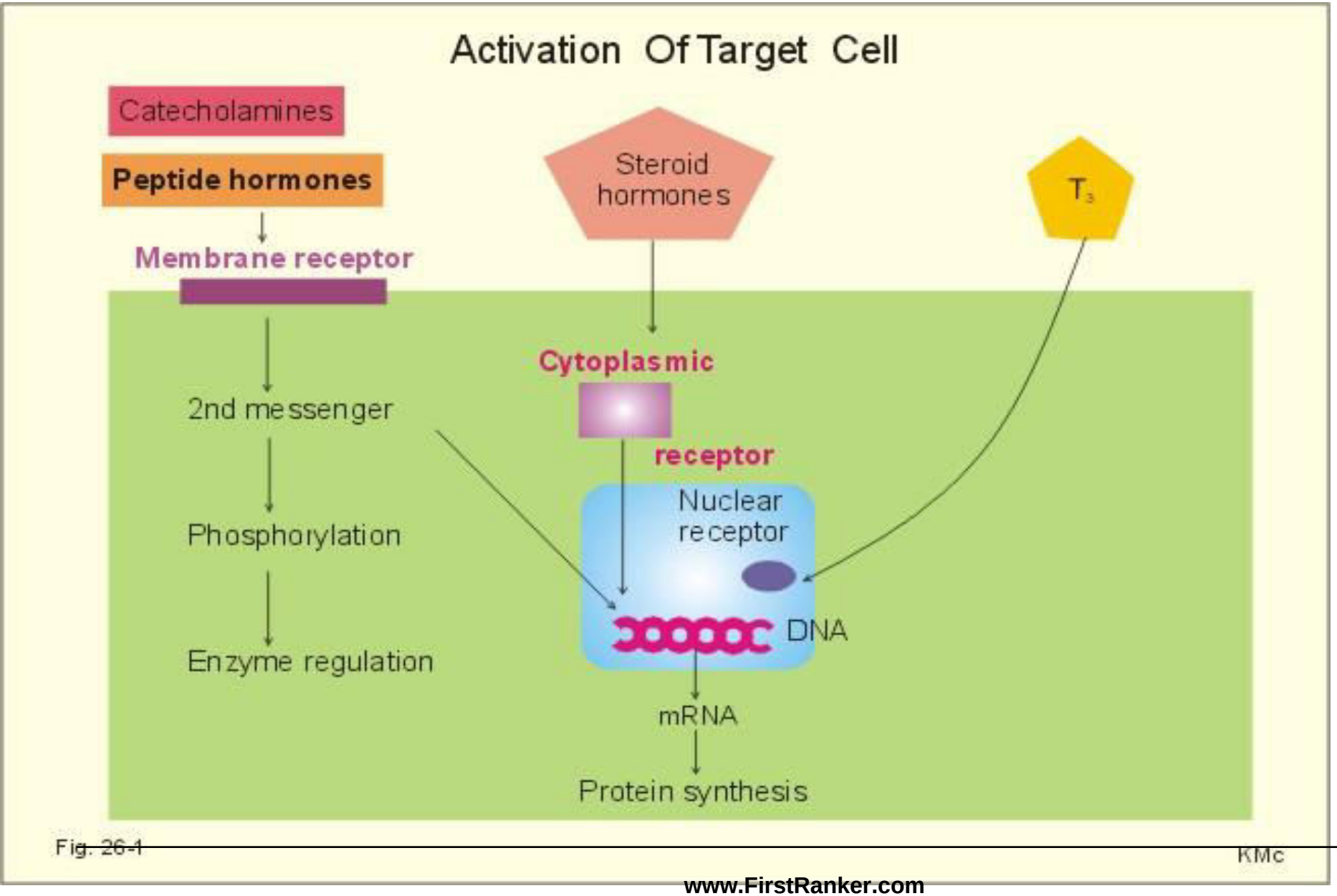


Fig. 26-1

KMc

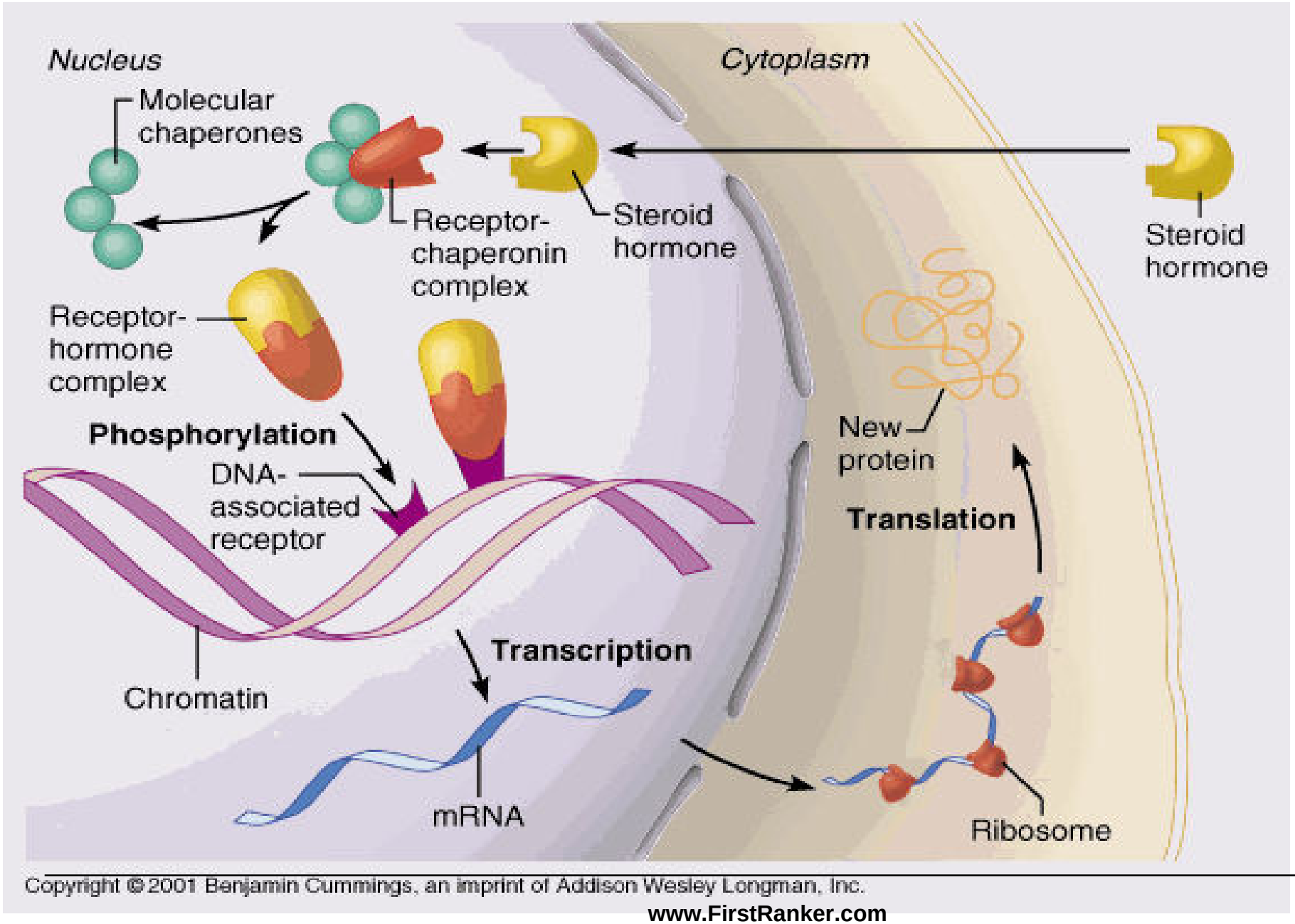
Steroid Hormones

- Steroid hormones are lipid soluble.
- Steroids can diffuse through the membrane
- They can cause:

Direct Gene Activation

- **Step-by-step**

1. Diffuse through the membrane
2. Binds & activates intracellular receptor.
3. Steroid-Receptor complex binds to DNA receptor protein
4. Activates a gene.
5. Gene transcribed into messenger RNA.
6. mRNA goes to the ribosomes
7. Translate mRNA into protein.



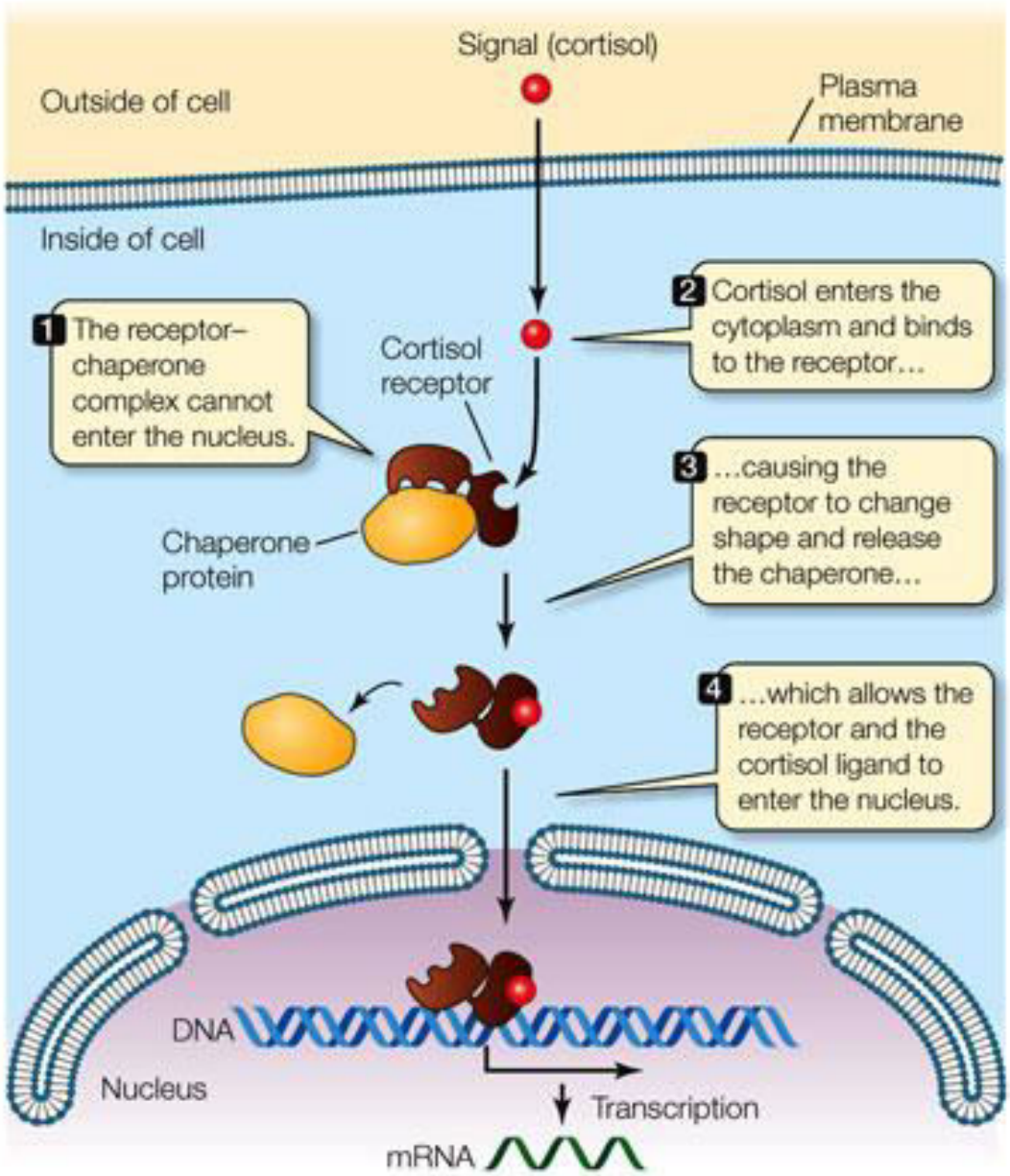
Cytoplasmic Receptors.

- Once inside the cell, they (Steroid hormones) bind **cytoplasmic receptors**.
- This causes receptor activation.
- Binding **dislodges** a protein that inhibits the expression of the gene at that segment (**heat shock 90 protein**).

- The hormone-receptors complex then enters the nucleus and binds to a particular sequence on the DNA.

- This sequence is called hormone response element (**HRE**).

- This receptor which has hormone bound to it and DNA sequence now serves as a binding site for other co activator proteins.
- Thus the gene begins to be transcribed and translated, and a new protein appears in the cell and assumes its normal function within it (or gets secreted).



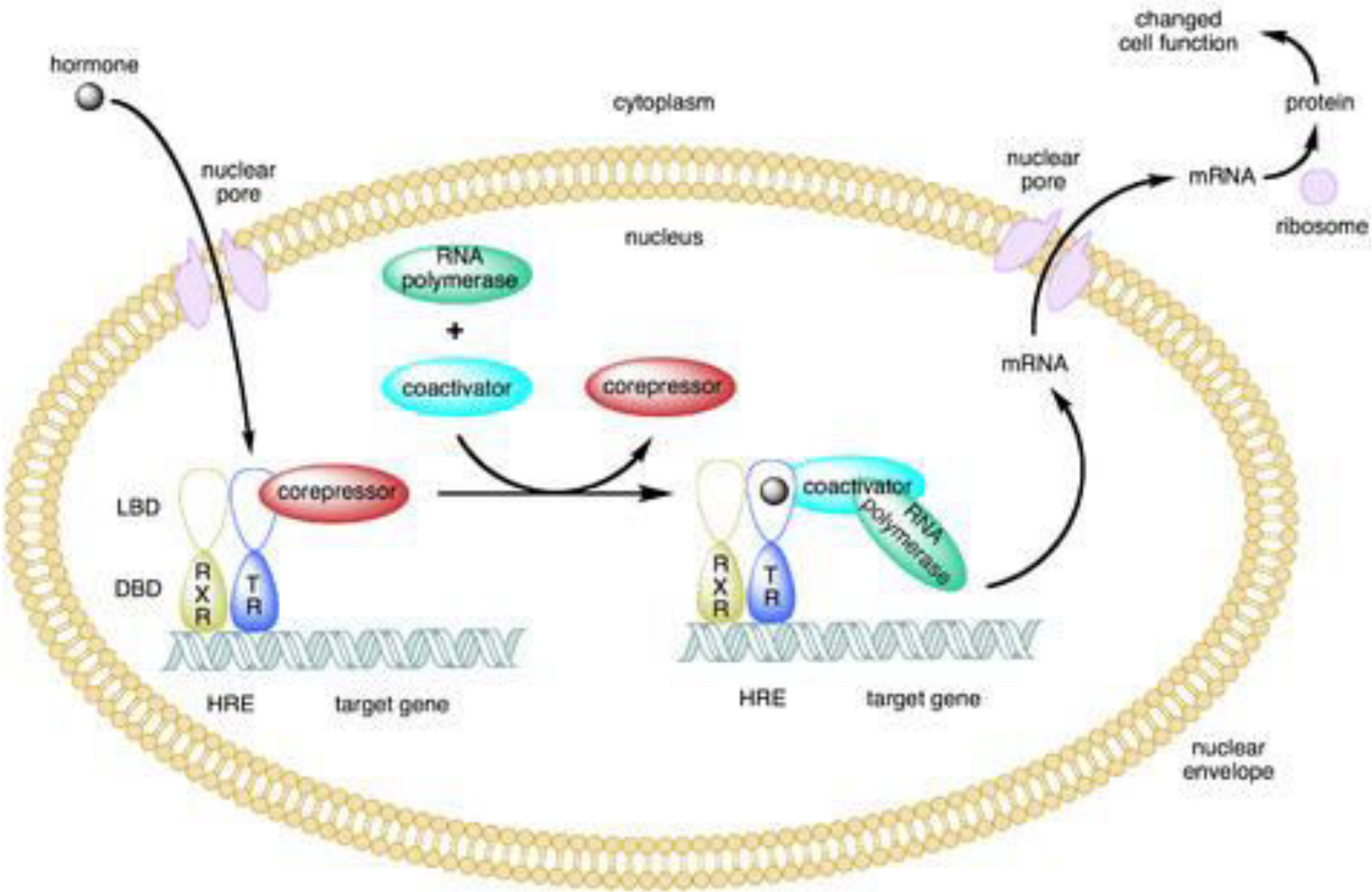
LIFE 8e, Figure 15.8

- In contrast hormones such as: Thyroid and Retinoids go **directly into the nucleus.**

- Their receptor is already bound to **HRE** (**hormone response element**), but along with a **co –repressor protein** which fails to activate transcription.

- The association of the ligand with the receptor results in the dissociation of the co repressor.

- Now this receptor- ligand complex can bind other co activator proteins and transcription begins.



- The **action of nuclear receptors is slow**, as it takes some hours for the whole process to occur. The **effect is long-lasting** (or even permanent) and changes the properties of the cell. This type of process is important in **development, differentiation and maturation of cells**, e.g. gametes (eggs and sperm cells).

Cell Surface Receptors

- There are three types of cell surface receptors:

1. Ion channel receptors

2. Transmembrane receptors

3. Receptors that are kinases or bind kinases.

Ion channel receptors:

- When a signaling molecule binds to an **ion channel** on the outside of the cell, this triggers the change of the 3D conformation of the protein and the channel opens, allowing the ions to move in or out of the cell following their electrical gradients and thus altering the polarization of the cell membrane..

- **voltage gated (ion) channel** - An integral membrane protein which is an ion channel within an excitable cell's outer cell membrane which opens and closes in response to a stimulus which is a change in membrane potential (voltage) [i.e., a change in local membrane charge from negative to positive or vice versa
- propagation in excitable cells such as neurons, muscle cells, and gland cells

- **chemically gated (ion) channel** - An integral membrane protein which is an ion channel within an excitable cell's outer cell membrane which opens and closes in response to a stimulus which is the arrival and binding of a specific ligand or signal molecule (hormone, neurotransmitter);

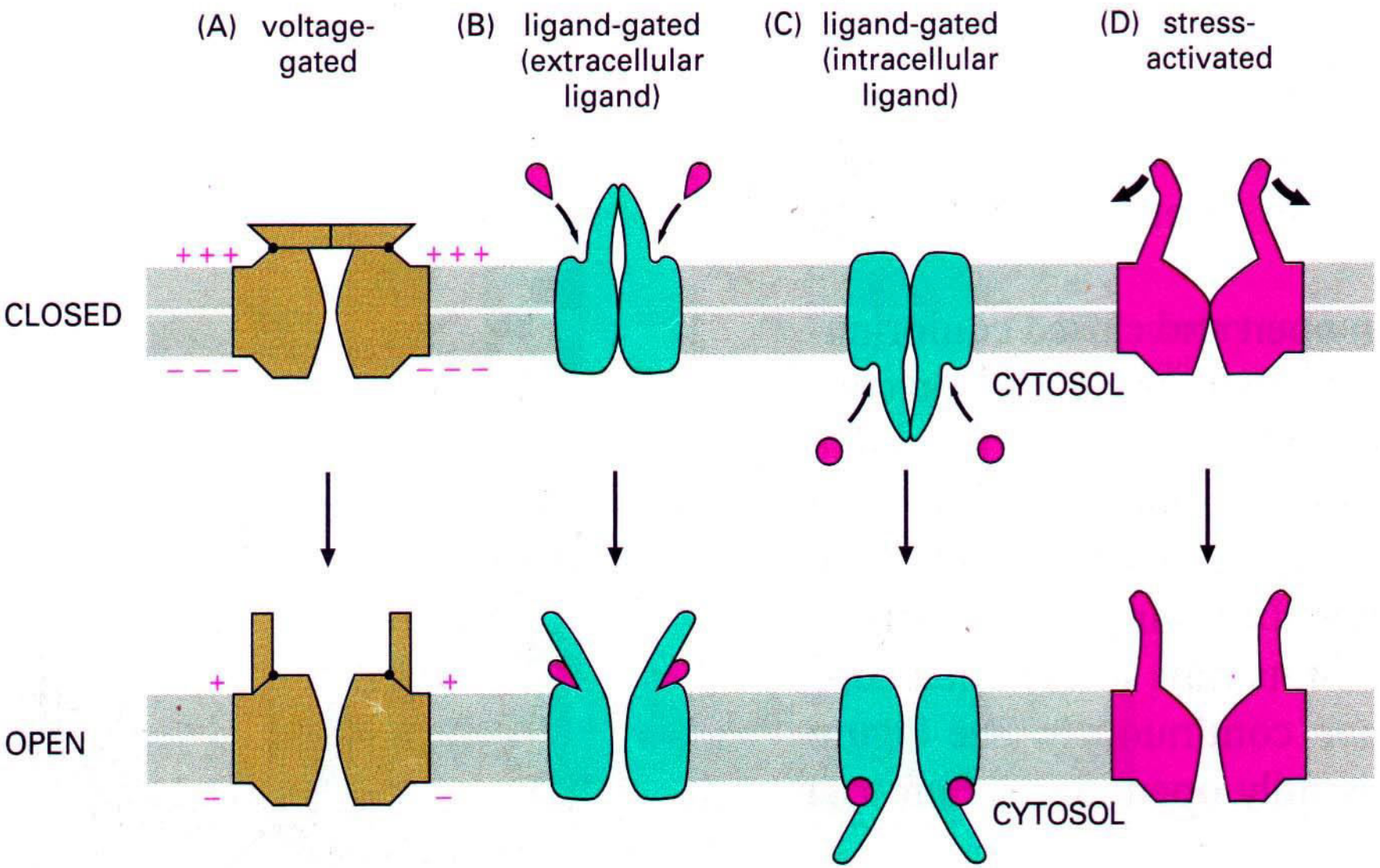
- excitable cell such as neurons, muscle cells, and gland cells.

- **light-gated (ion) channel** - An integral membrane protein which is an ion channel within a photosensitive excitable cell's outer cell membrane which opens in response to a stimulus which is the arrival of a photon of light energy;

- photoreceptor (sensory cells- rods and cones responding to light in the retina of the eye).

- **mechanically gated (ion) channel** - An integral membrane protein which is an ion channel within an excitable cell's outer cell membrane which opens and closes in response to a stimulus which is a mechanical pressure or vibration;

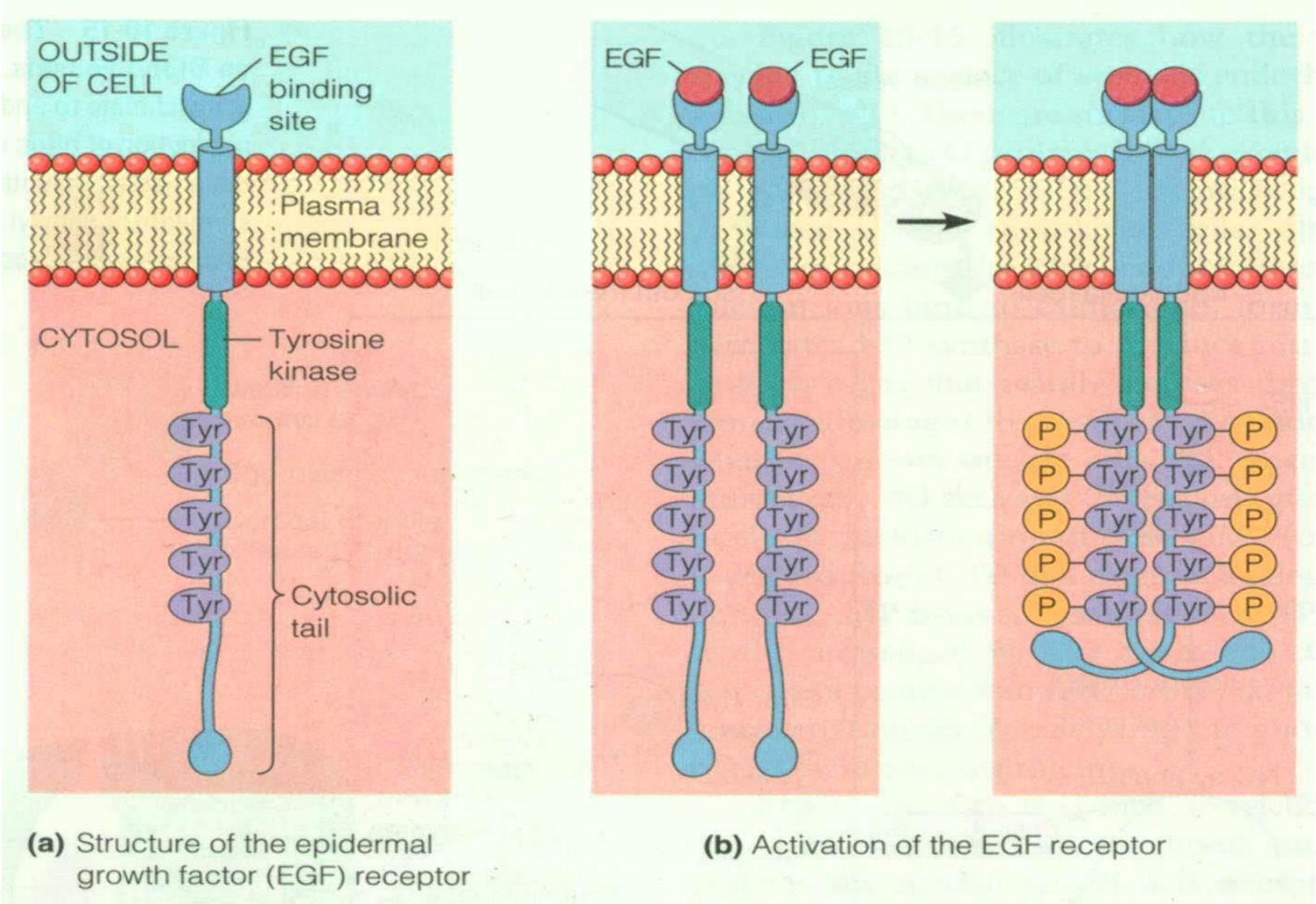
- mechanoreceptor (sensory cell responding to touch, vibration, compression or stretch).



Receptors that are kinases or bind kinases:

- When a signaling chemical binds to the **membrane receptor** protein on the outside of the cell, this triggers a change in the 3D conformation of that protein, which in turn, triggers a chemical reaction on the inside of the cell.

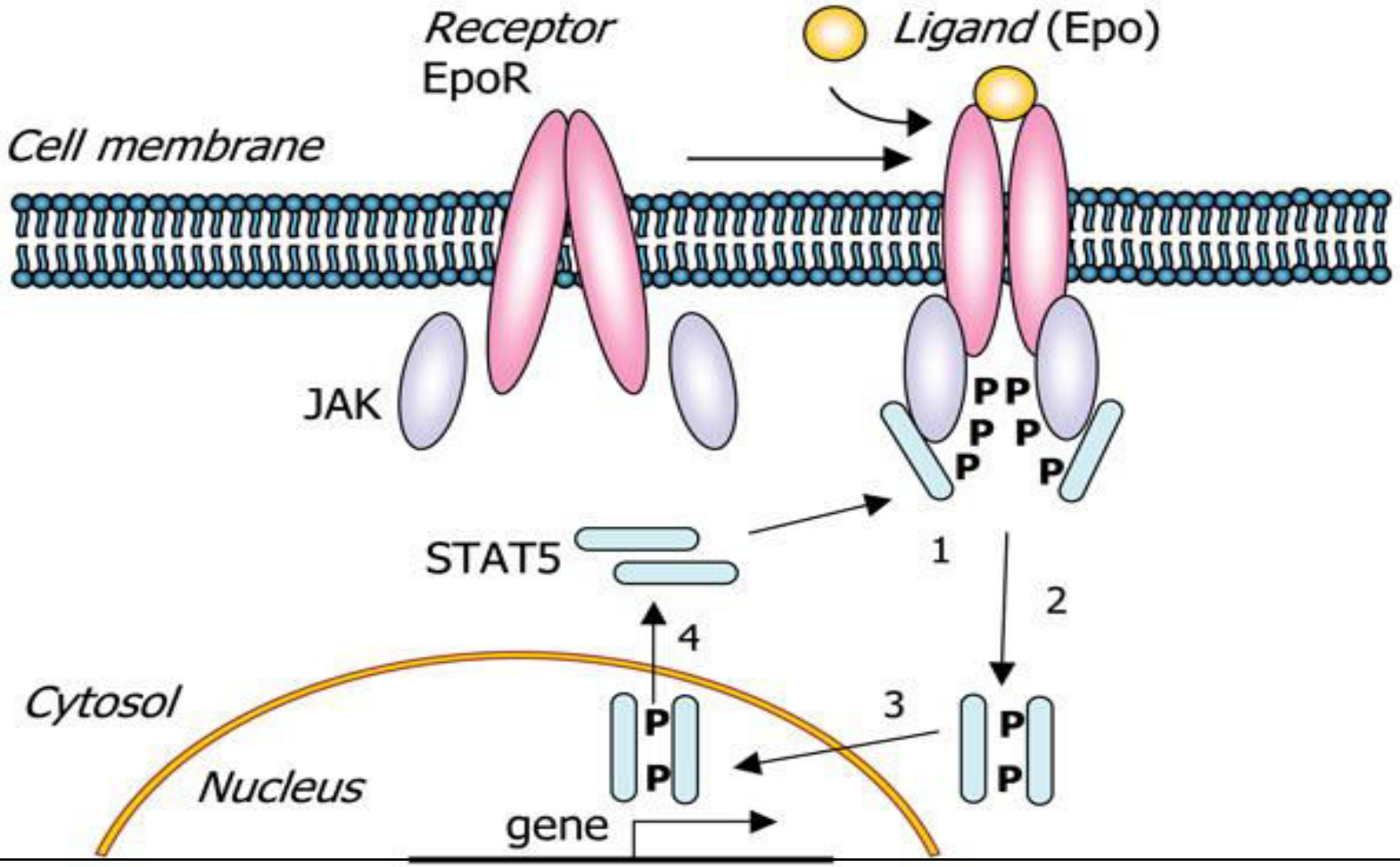
- Their main features is that the intracellular domain of the receptor is a **kinase**, that is activated when the messenger binds to the extracellular domain.
  Receptor kinase **phosphorylates** an amino acid residue that is present on the receptor or an associated protein.
- Message is transmitted through signal transducer proteins.



(a) Structure of the epidermal growth factor (EGF) receptor

(b) Activation of the EGF receptor

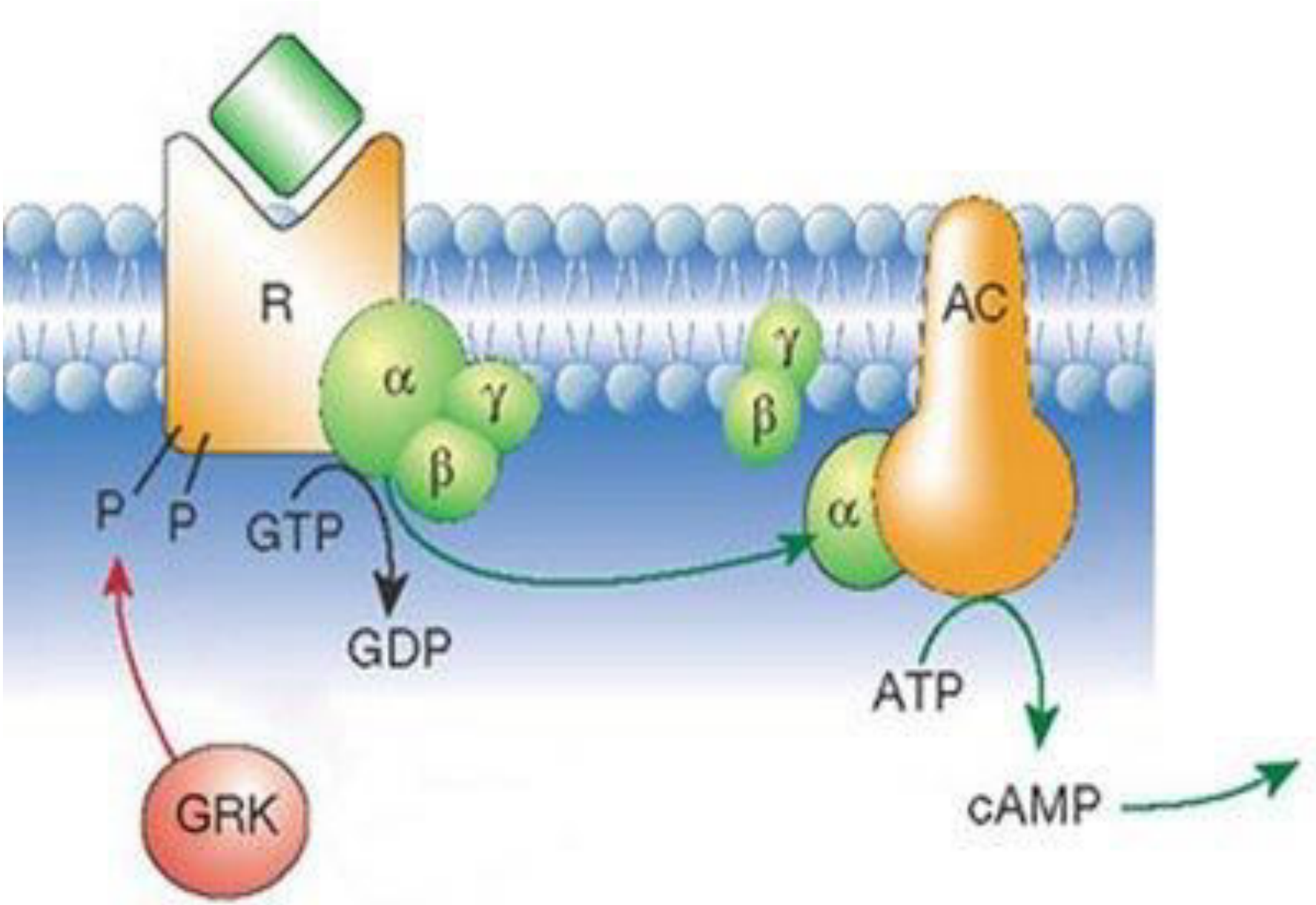
Jak-Stat pathway

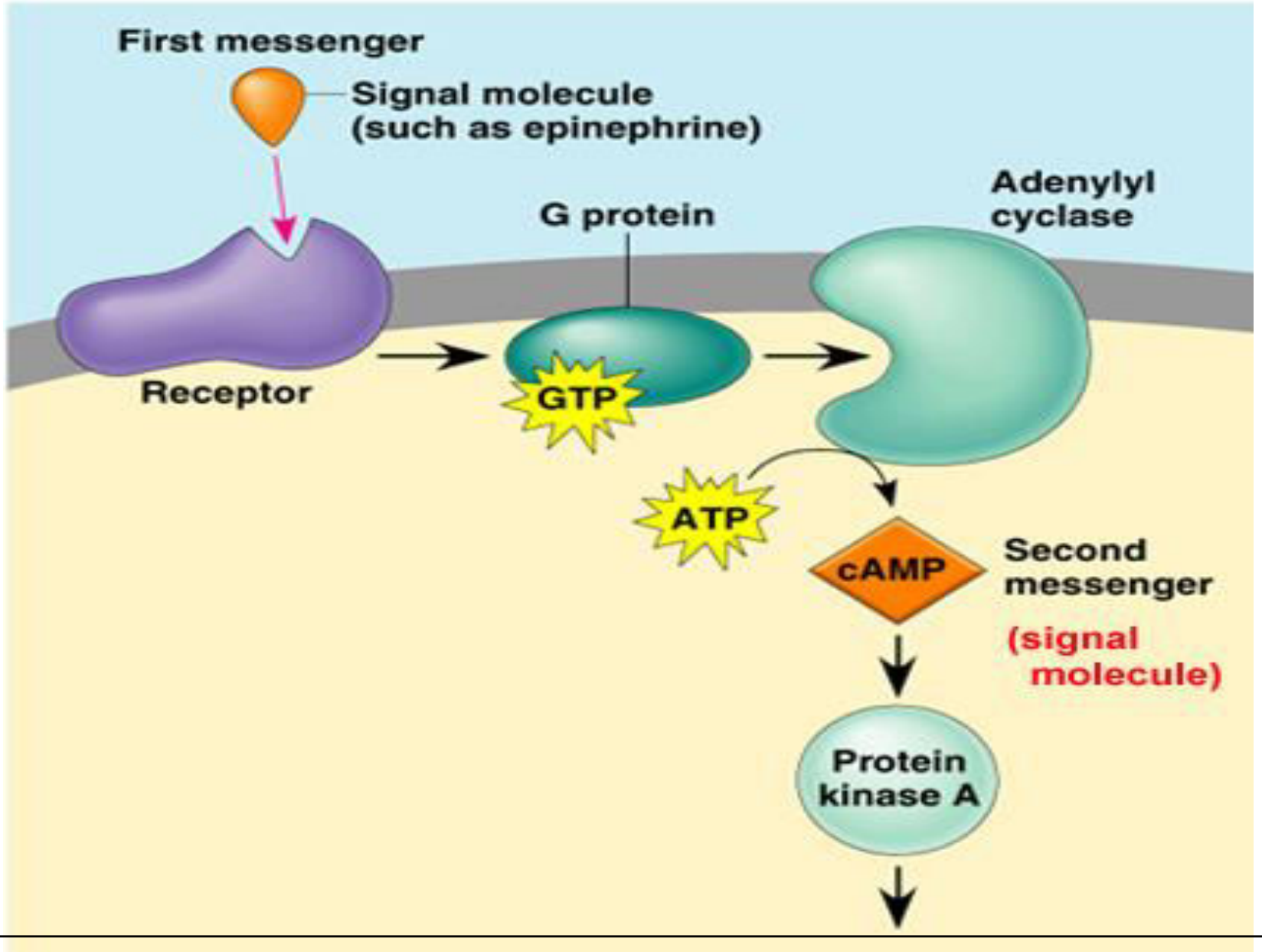


- **Transmembrane proteins** include **G protein-linked receptors** and they are seven-pass trans membrane proteins.
- This means that the polypeptide chain traverses the membrane seven times. When a chemical - a hormone or a pharmaceutical agent - binds to the receptor on the outside of the cell, this triggers a series of chemical reactions:

- including the movement and binding of the G-protein.
- transformation of GDP into GTP and
- activation of second messengers.

- Second messengers (e.g., cyclic AMP) start a cascade of enzymatic reactions leading to the cellular response. This signaling method is quite fast and, it amplifies the signal.




First messenger
Signal molecule
(such as epinephrine)
G protein
Adenylyl
cyclase
Receptor
GTP
ATP
cAMP
Second
messenger
(signal
molecule)
Protein
kinase A

G- protein receptors

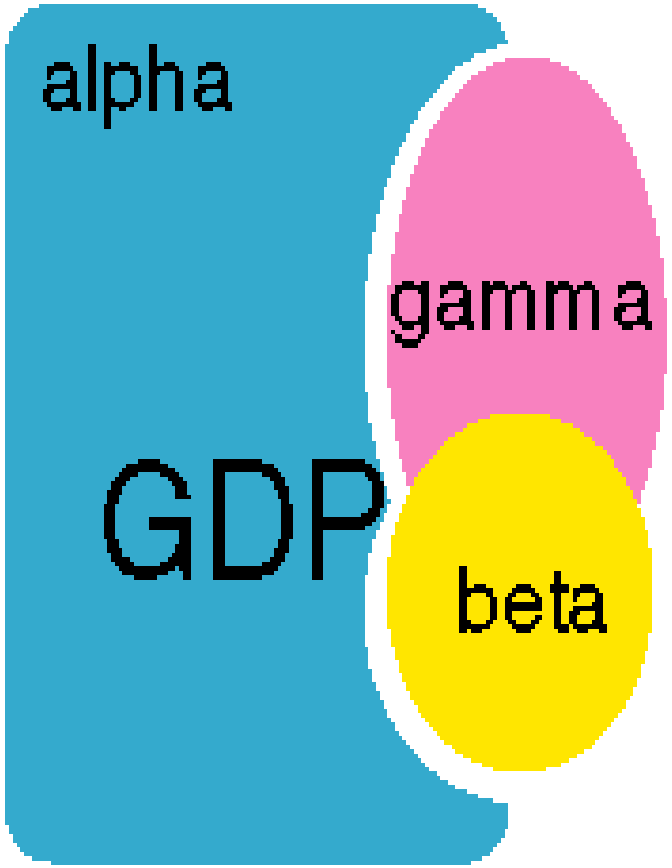
A. **Basic G-protein Receptor**

1. whole family of receptors
2. All use same basic pattern

a. ligand binds to receptor (outer surface of cell).

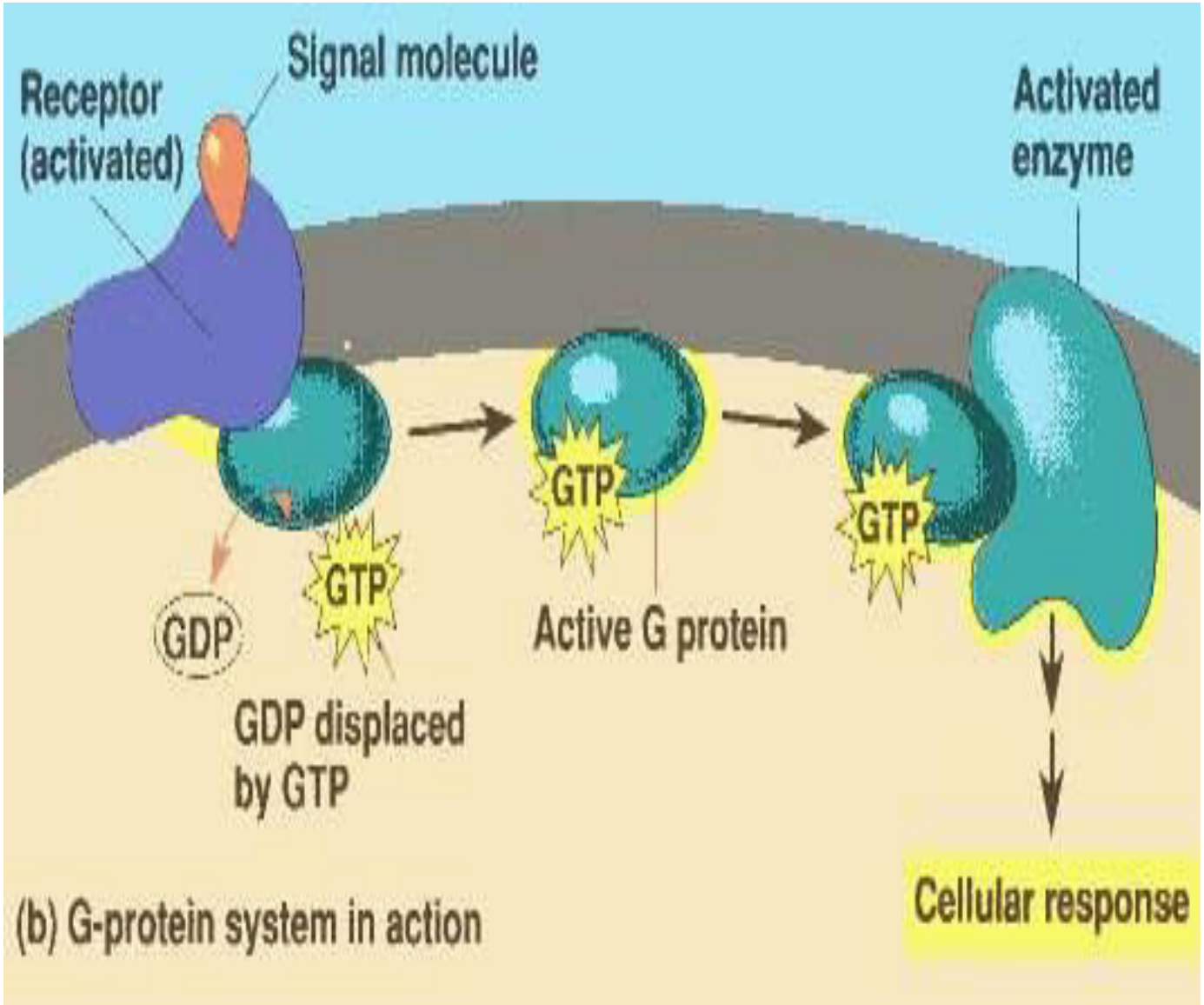
b. receptor **changes shape** (inner surface of cell).

- shape change allows receptor **to bind inactive G-protein**
- **inactive G-protein = G-alpha + GDP + G-beta + G-gamma**



Inactive Heterotrimeric G-protein

- **inactive G-protein binds** to receptor
- **receptor activates G-protein**
- G-alpha drops GDP, picks up GTP
- when G-alpha binds GTP --> G-beta and G-gamma are released.


Receptor
(activated)
Signal molecule
Activated
enzyme
GTP
GTP
GTP
GDP
Active G protein
GDP displaced
by GTP
Cellular response
(b) G-protein system in action

- G-alpha + GTP is released from receptor into cytoplasm
- G-alpha + GTP = active G-protein.
- activated G-protein binds to target protein target protein's activity is altered - might be stimulated or might be inhibited .

Adenylyl Cyclase

- Different peptide hormones can either stimulate or inhibit the production of cAMP from adenylyl cyclase.

- There are two parallel systems that converge upon a single catalytic molecule – (C).

- These parallel systems are inhibitory or stimulatory.

- Each consists of a receptor and (**R** -Rs or Ri) and a regulatory complex (**G**- Gs or Gi).

- G-complex is again composed of three subunits- α,β and γ.
- It is basically the α-subunit that is either stimulatory or inhibitory.
- α-subunit binds the GDP or GTP.

- When the hormone binds to the receptor conformational change occurs in the G complex and it binds GTP instead of GDP.

- This binding occurs to the α-subunit and it dissociates from β and γ subunit.

- The **αs** protein has intrinsic GTPase activity and it catalyses the conversion of GTP- GDP,
- The three subunits again recombine, and is again ready for another cycle of activation.

- **Cholera and Pertussis** toxins catalyze ADP ribosylation of **αs** and **αi-2**.

- Due to which in **αs** intrinic GTPase activity is disrupted and it cannot associate with its other subunits.

- In the **αi-2** dissociation is prevented, and αs activity is un opposed.

- GPCRs are implicated in a number of diseases and are major targets for the pharmaceutical companies.

Clinical applications of hormones

- Distribution of estrogens and progesterone in *contraceptives* (P pills) is world-wide. Estrogens are widely used to relieve postmenopausal discomfort.
- Females with osteoporosis are treated with calcitonin, because calcitonin inhibits osteoclastic bone resorption.
- Insulin is a lifesaver for diabetics, and it is produced and distributed as pure human insulin.

- In the affluent areas of the world many women deliver their babies following an oxytocin infusion.
- estrogens and gonadotropins are used in treatment of sterility and menstrual disturbances.
- Huggins received the Nobel Prize in 1966 for the introduction of a new form of cancer therapy in which sex hormones are used to retard their growth. He used androgens for breast cancer and estrogens for prostate cancer.