

# SIGNAL TRANSDUCTION

# Cell-Cell Interactions

- For a coordinated function of cells in a tissue, tissues in an organ, organs in a system and systems in the body, cells need to be able to communicate with each other.
- Each cell should be capable of sending chemical signals to other cells and of receiving chemical signals from other cells, as well as signals (chemical or other) from its immediate environment.

- A cell can communicate signals to other cells in various ways.
- **Autocrine signaling**
- **Paracrine signaling**
- **Endocrine signaling**
- **Direct signaling**
- **Synaptic signaling**

# Autocrine signaling

- is a way for a cell to alter its own extracellular environment, which in turn affects the way the cell functions. The cell secretes chemicals outside of its membrane and the presence of those chemicals on the outside modifies the behavior of that **same cell**. This process is important for **growth**.

# Paracrine signaling

- is a way for a cell to affect the behavior of **neighboring cells** by secreting chemicals into the common intercellular space. This is an important process during **embryonic development**.

# Endocrine signaling

- **utilizes hormones.** A cell secretes chemicals into the bloodstream. Those chemicals affect the behavior of **distant target cells.**

# Direct signaling

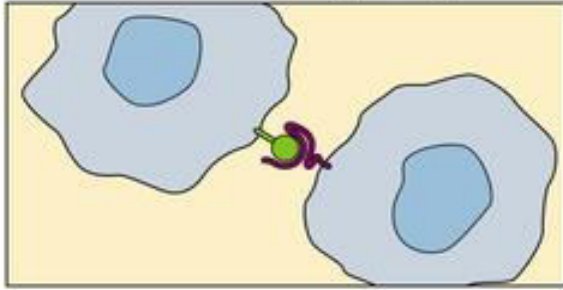
- is a transfer of ions or small molecules from **one cell to its neighbor through pores in the membrane**. Those pores are built out of membrane proteins and are called **gap junctions**. This is the **fastest mode** of cell-cell communication and is found in places where extremely fast and well-coordinated activity of cells is needed. An example of this process can be found in the **heart**. The muscle cells in the heart communicate with each other via gap junctions which allows all heart cells to contract almost simultaneously.

# Synaptic signaling

- is found in the **nervous system**. It is a highly specific and localized type of paracrine signaling between **two nerve cells** or between **a nerve cell and a muscle cell**.

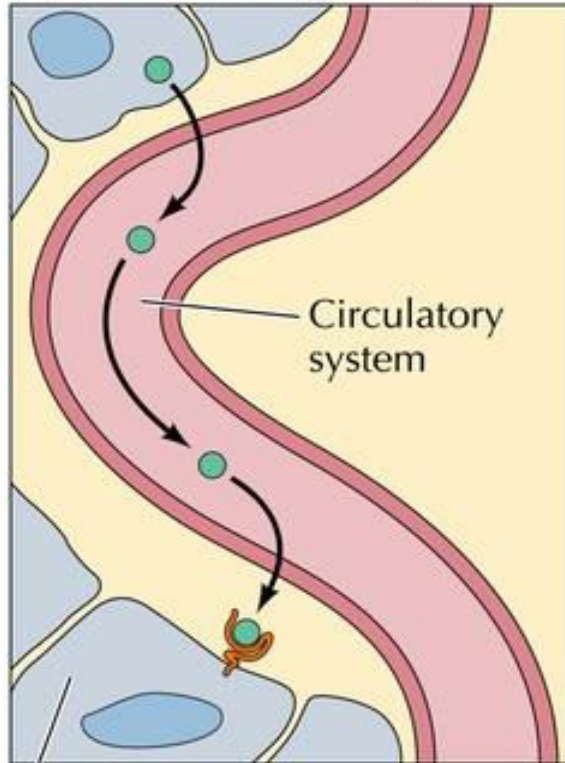


### Direct Cell-Cell Signaling



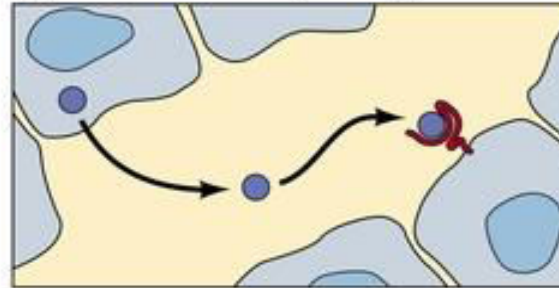
### Signaling by Secreted Molecules

(A) Endocrine signaling

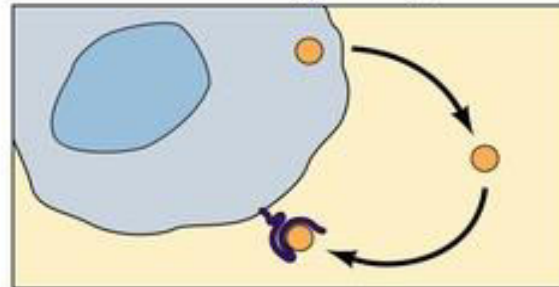


Target cell

(B) Paracrine signaling



(C) Autocrine signaling



# Target cells

**Specific cells are affected by hormone and respond in unique fashion:**

- Cells have specific receptors on membrane or in cell that respond to hormone
- Can have receptors for several different hormones
- Number of active receptors can change
  - ▣ Down-regulation - number of receptors decreases & target is less sensitive
  - ▣ Up-regulation - number increases & target is more sensitive

# How does a cell receive a signal?

- Some small molecules are capable of entering the cell through the plasma membrane.
- Some small hormones also enter the cell directly, by passing through the membrane. Examples are steroid hormones and thyroid hormones.

# HORMONES



- Hormones are the chemical messengers of the body. They are defined as **organic substances** secreted into blood stream to control the metabolic and biological activities.

- These hormones are involved in transmission of information from one tissue to another and from cell to cell. These substances are produced in small amounts by various endocrine (ductless) glands in the body.

- They are **delivered directly to the blood in minute quantities** and are carried by the blood to various target organs where these exert physiological effect and control metabolic activities. Frequently their site of action is away from their **origin.**

- Hormones are required in **trace amounts** and are **highly specific** in their functions. The deficiency of any hormones leads to a particular disease, which can be cured by administration of that hormone.

Hormones are released **continuously** or in **short bursts**, amount and frequency can vary. Circulating hormones are transported by blood in solution or attached to plasma proteins.



Local hormones remain in interstitial fluid and act on nearby cells. Hormones produce **slower response** than nervous system but longer lasting effects. Hormones are **inactivated by liver & excreted by kidneys.**




□ **Functions:**

- Stimulate synthesis of enzymes or structural proteins.
  
- Change rate of synthesis.
  
- Inactivate or activate existing enzymes or protein channels.

# Target cells sensitive to several hormones may show interactive effects.

1. **Permissive effects** - first hormone enhances the effect of a later hormone action: example:
  - Estrogen up-regulates progesterone receptors in uterus
  - Thyroid hormone increases the effect of epinephrine on breakdown of triglycerides in adipocytes.



**2. Integrative effects** - hormones produce complementary effects on different tissues:

Example:

- PTH and calcitriol increase ECF calcium.

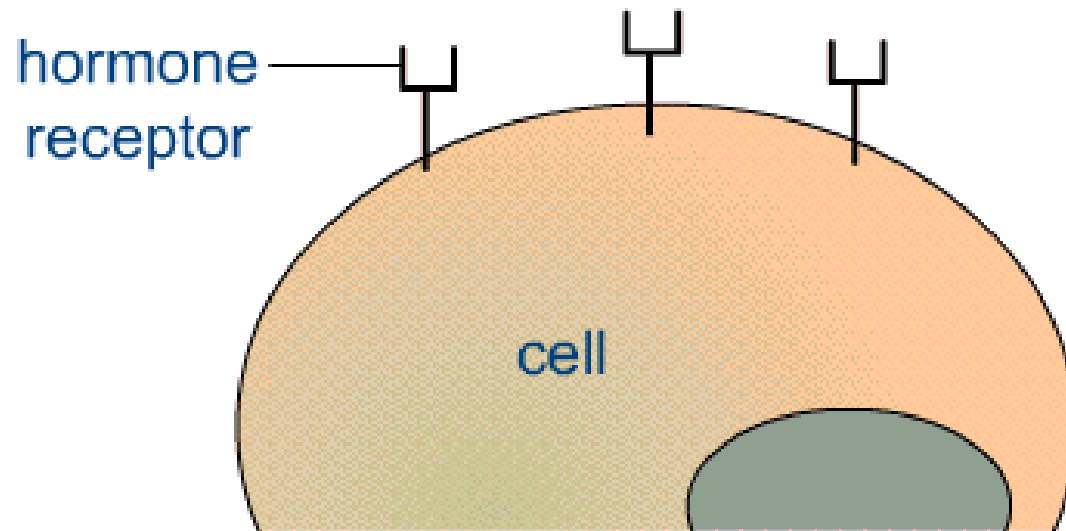
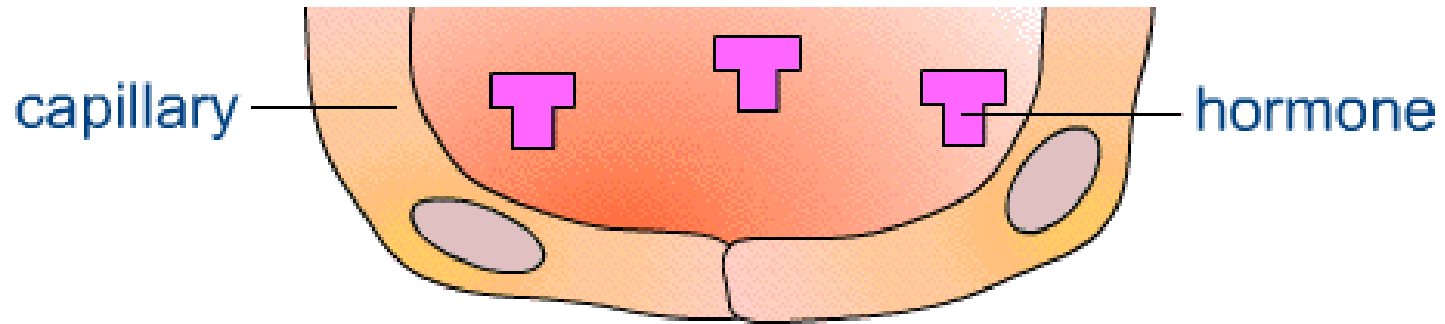
**3. Synergistic effects** - two hormones acting together have a greater effect than the sum of the effects of each hormone acting independently. Example:

- Both FSH and estrogen necessary for normal oocyte development.
- FSH and testosterone together increase spermatogenesis than alone.



4. **Antagonistic effects** - one hormone opposes the action of the other hormone. Example:

- Insulin and glucagon.



# 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

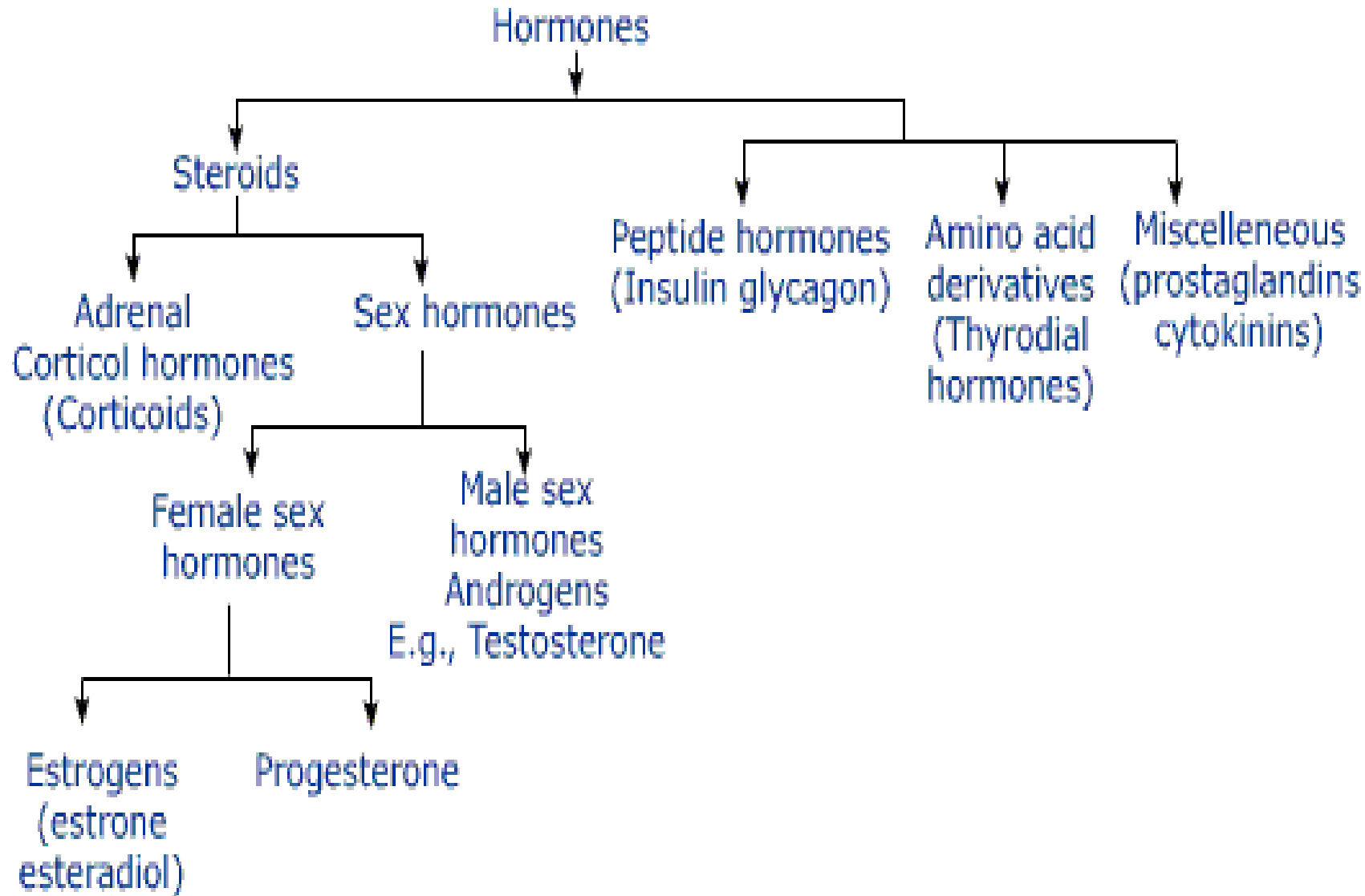
**Plasma half life-** Short

**Receptor-** Plasma membrane

**Mediator-** cAMP, cGMP, Calcium and phosphatidylinositol.

# Classification of Hormones

- Hormones are classified on the basis of:
  - (i) **Their structure.**
  - (ii) **Their site of activity in the cell.**



# Steroid hormones

1. Sex hormones - are divided into 3 groups

(i) Male sex hormones or Androgens

(ii) Female sex hormones or Estrogens

(iii) Pregnancy hormones or Progestines.

2. Hormones of Adrenal Cortex

# Non steroid hormones

## 1. Peptide hormones-

- E.g. all hypothalamic, anterior pituitary, digestive hormones

## 2. Amino acid derivatives

- Amines - simplest form, derived from tyrosine or tryptophan
- E.g. TH, dopamine, epinephrine, melatonin

Hypothalamus functions as master co-ordinator of hormonal action. It produces at least 6 releasing factors or hormones.

- ❑ Thyrotropin releasing hormone (TRH)
- ❑ Corticotropin releasing hormone (CRH)
- ❑ Gonadotropin releasing hormone ( $G_n$ RH)
- ❑ Growth hormone releasing hormone (GRH)
- ❑ Growth hormone release inhibiting hormone (GRIH)
- ❑ Prolactin release inhibiting hormone (PRIH)

# 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.**



- 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 effector mechanism in the cell .



- Selectivity

- Effector mechanism- receptor has got two domains.

1. Binding domain
2. Signal generation domain

(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.

## Activation Of Target Cell

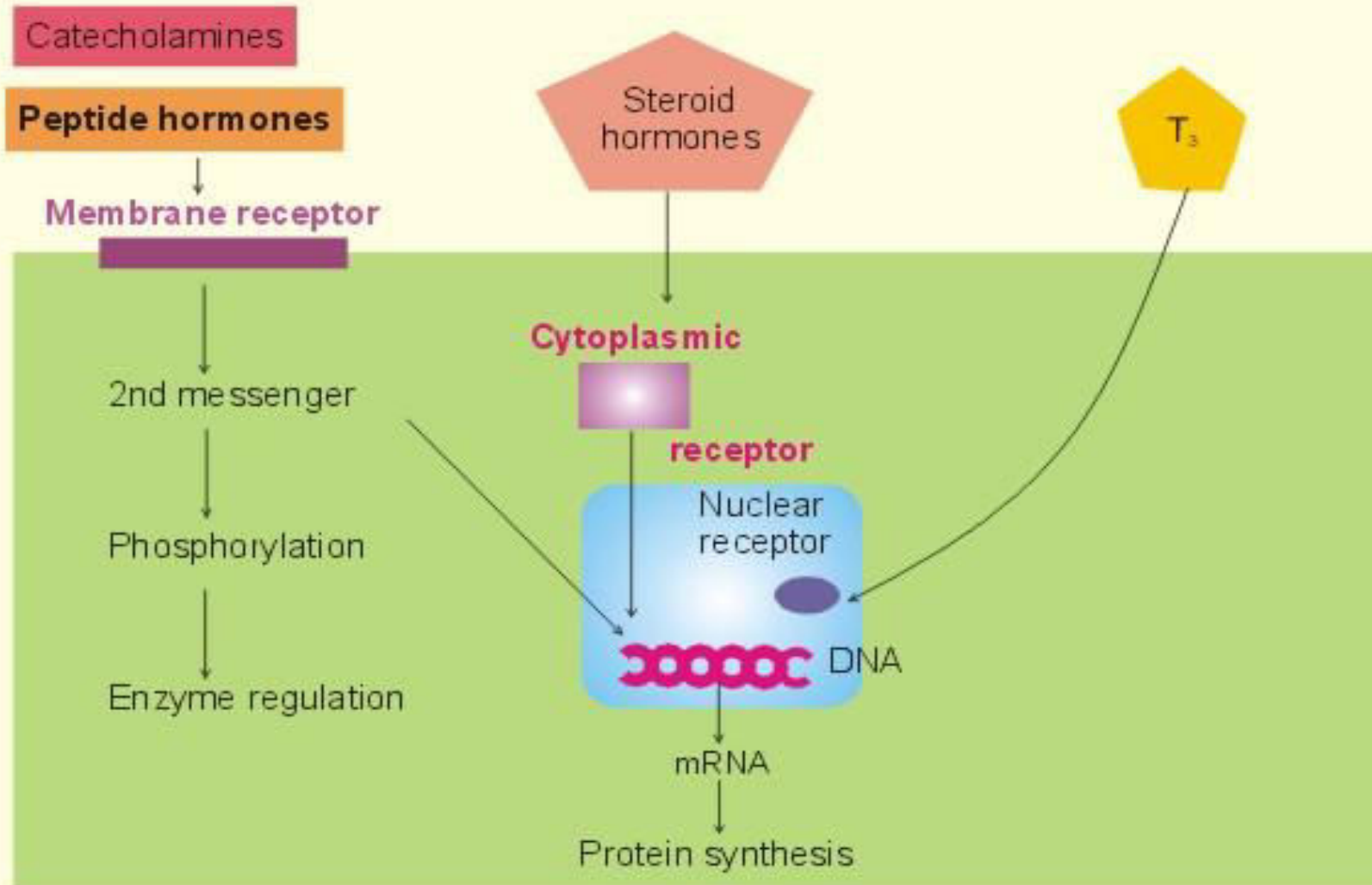


Fig. 26-1

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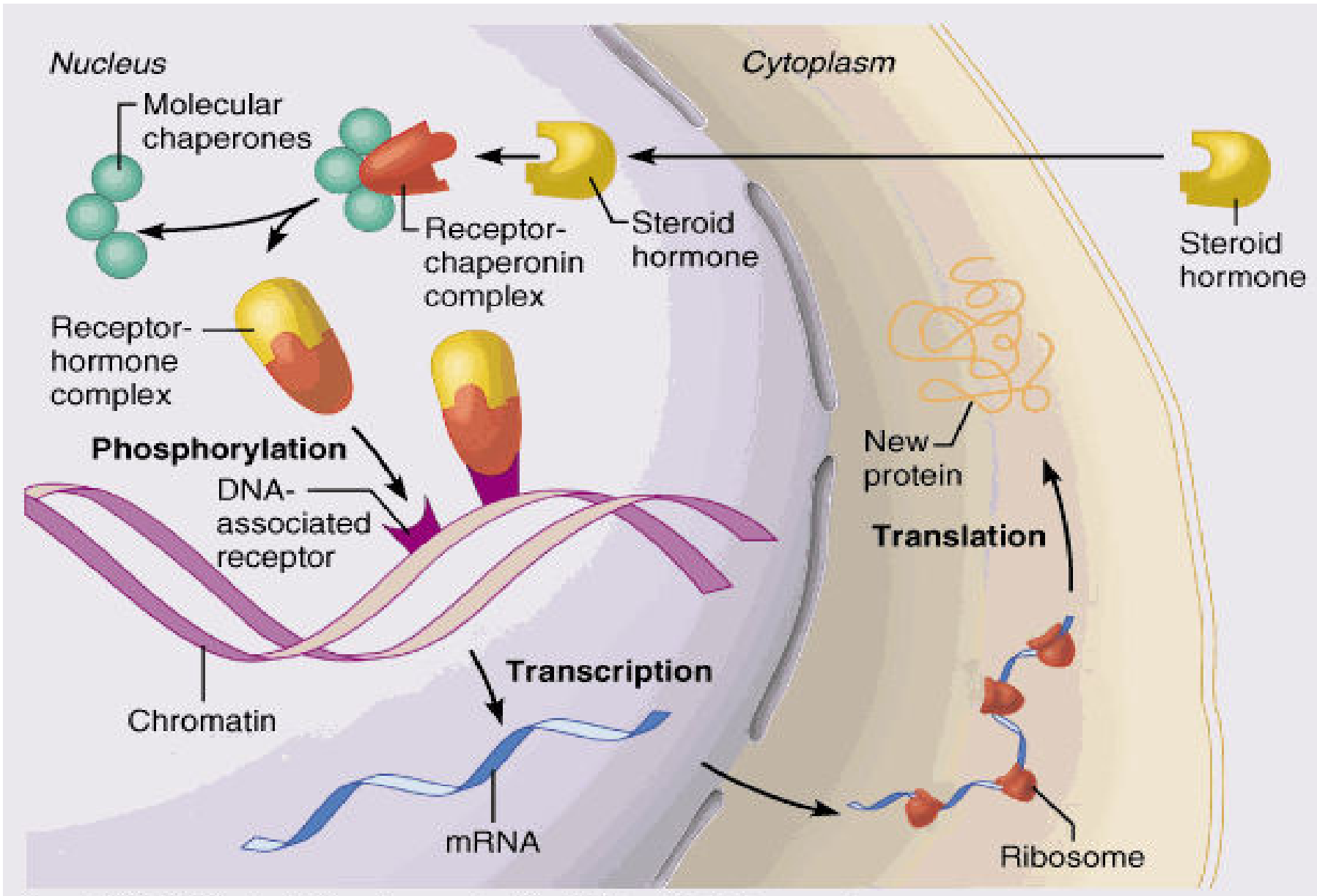
# Steroid Hormones

- ❑ 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.



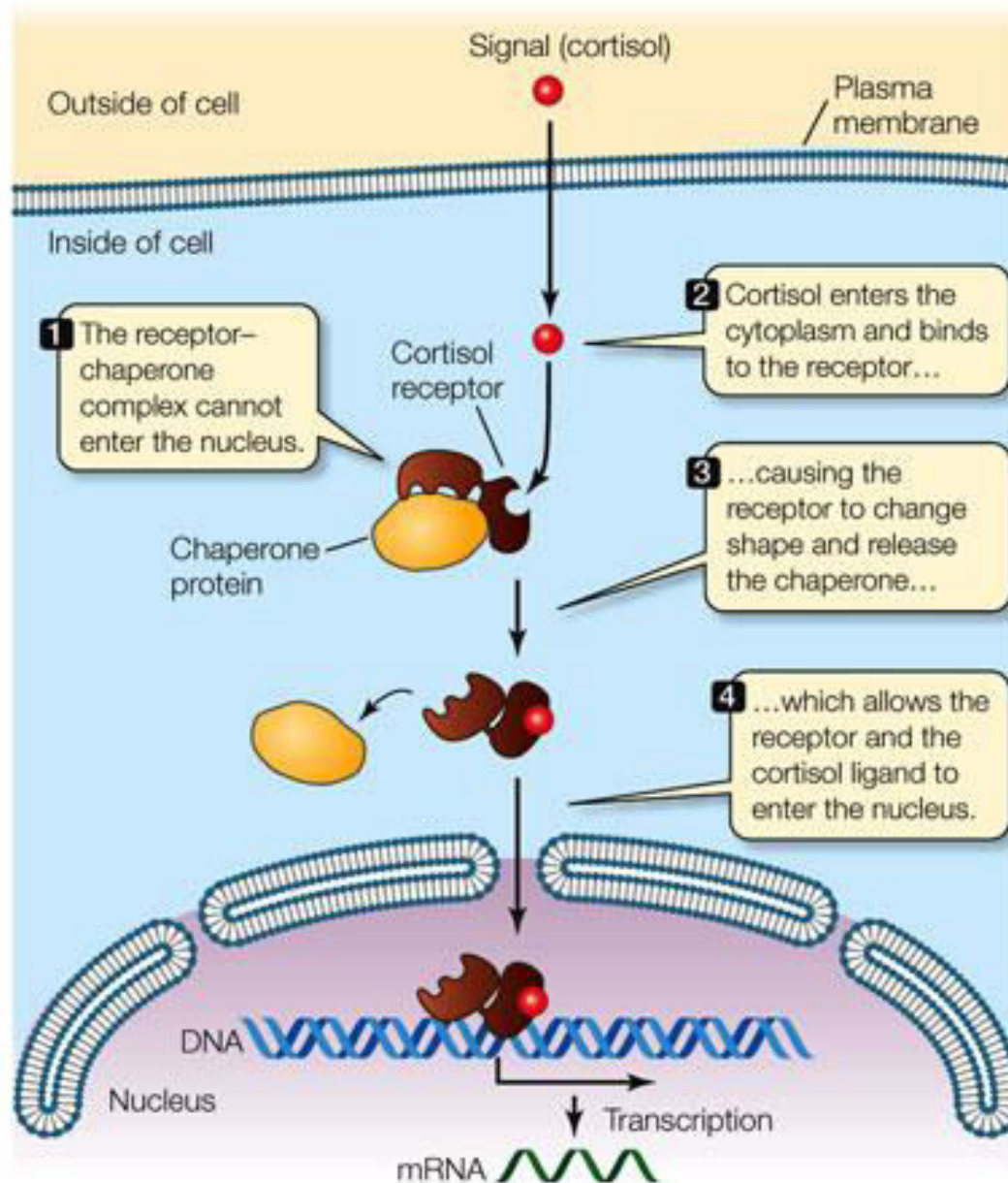
# Cytoplasmic Receptors.

- 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).

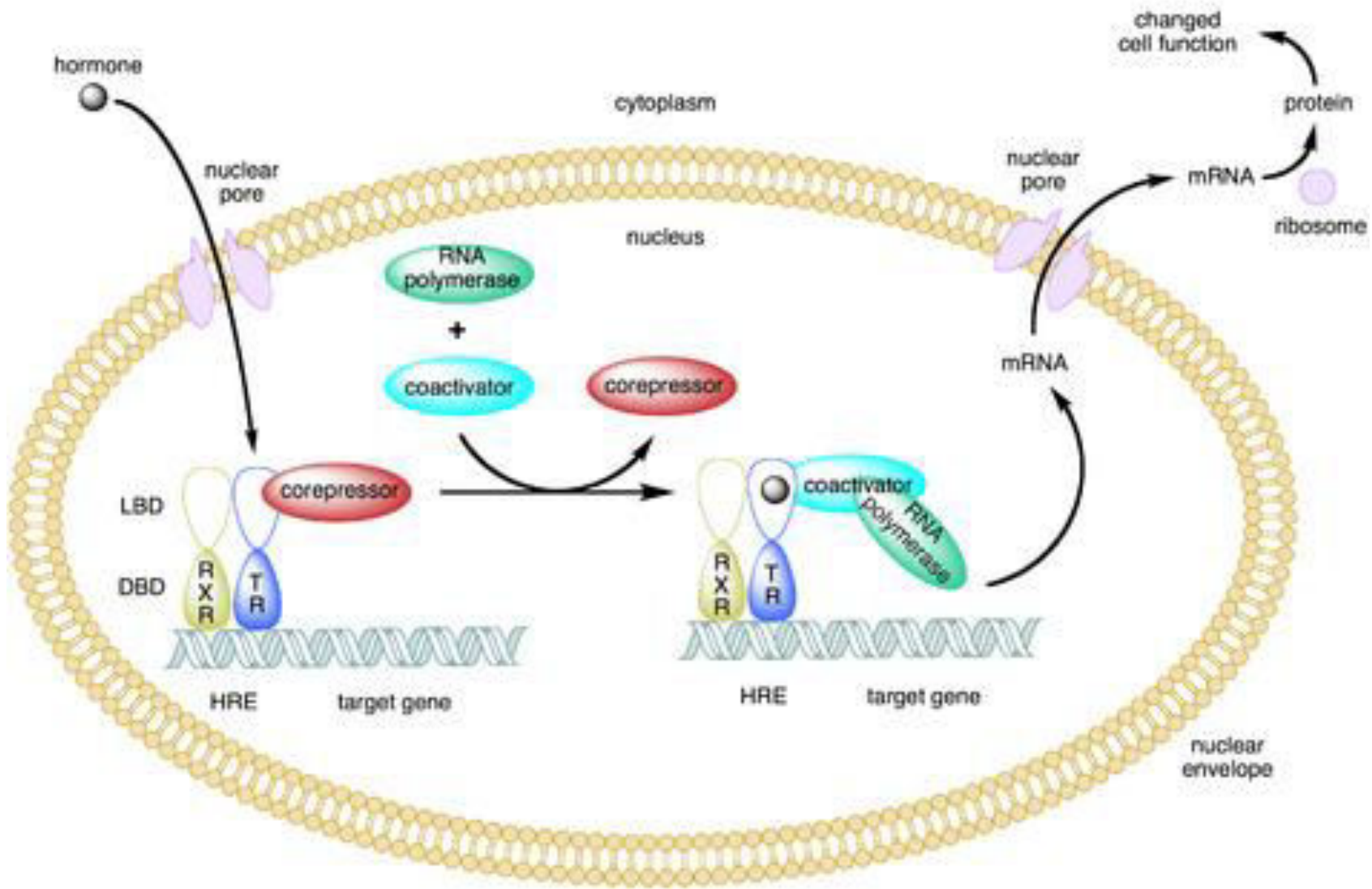


LIFE 8e, Figure 15.8

- 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).

- In contrast hormones such as: Thyroid and Retinoids go directly into the nucleus.
- Their receptor is already bound to HRE, 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.



# 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. Some ion channels respond to non-chemical stimuli in the same way, including changes in electrical charge or mechanical disturbance of the membrane.

## Receptors that are kinases or bind kinases:

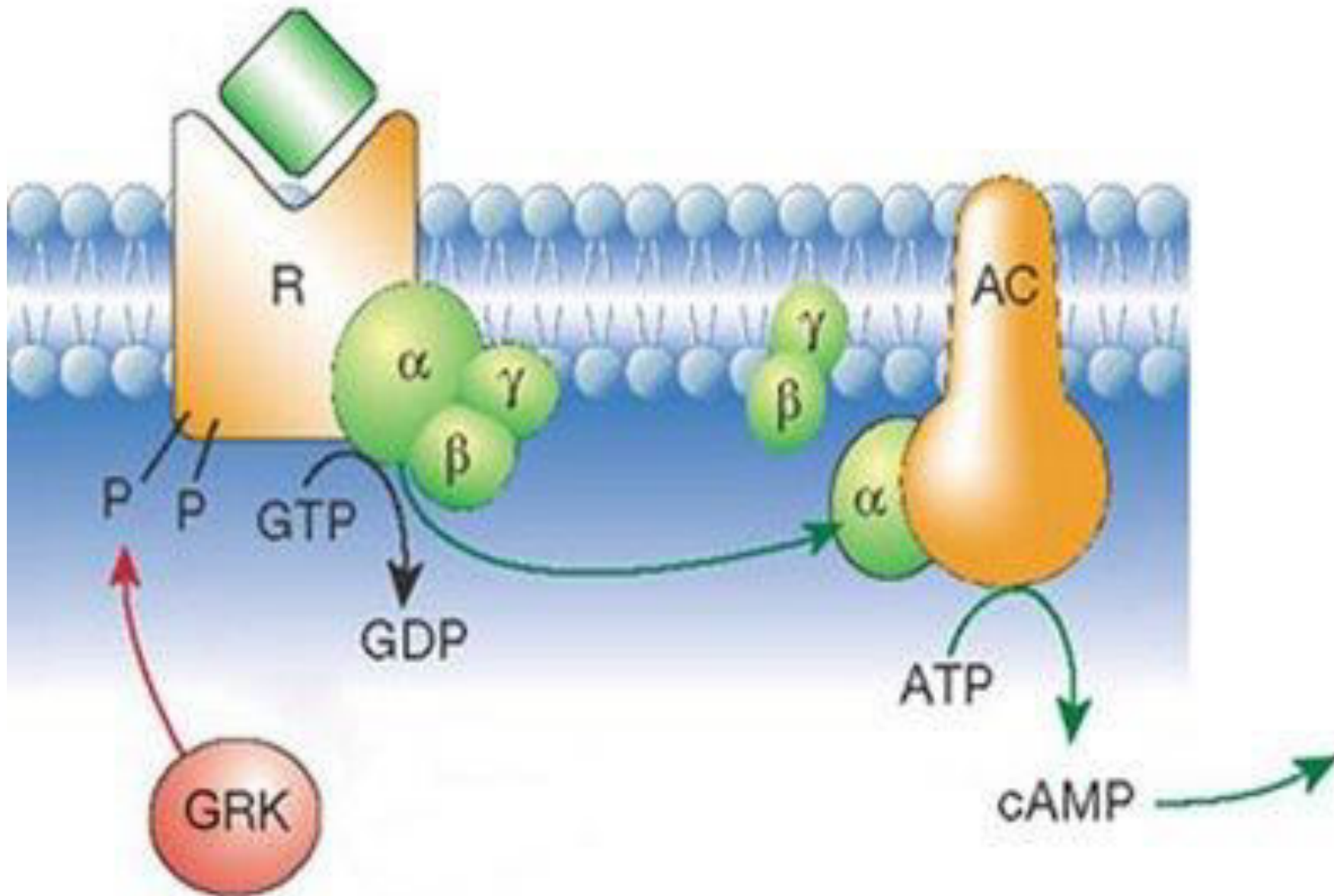
- When a signaling chemical binds to the **membrane receptor** protein on the outside of the cell, this triggers a change in the 3D conformation of that protein, which in turn, triggers a chemical reaction on the **inside of the cell**.

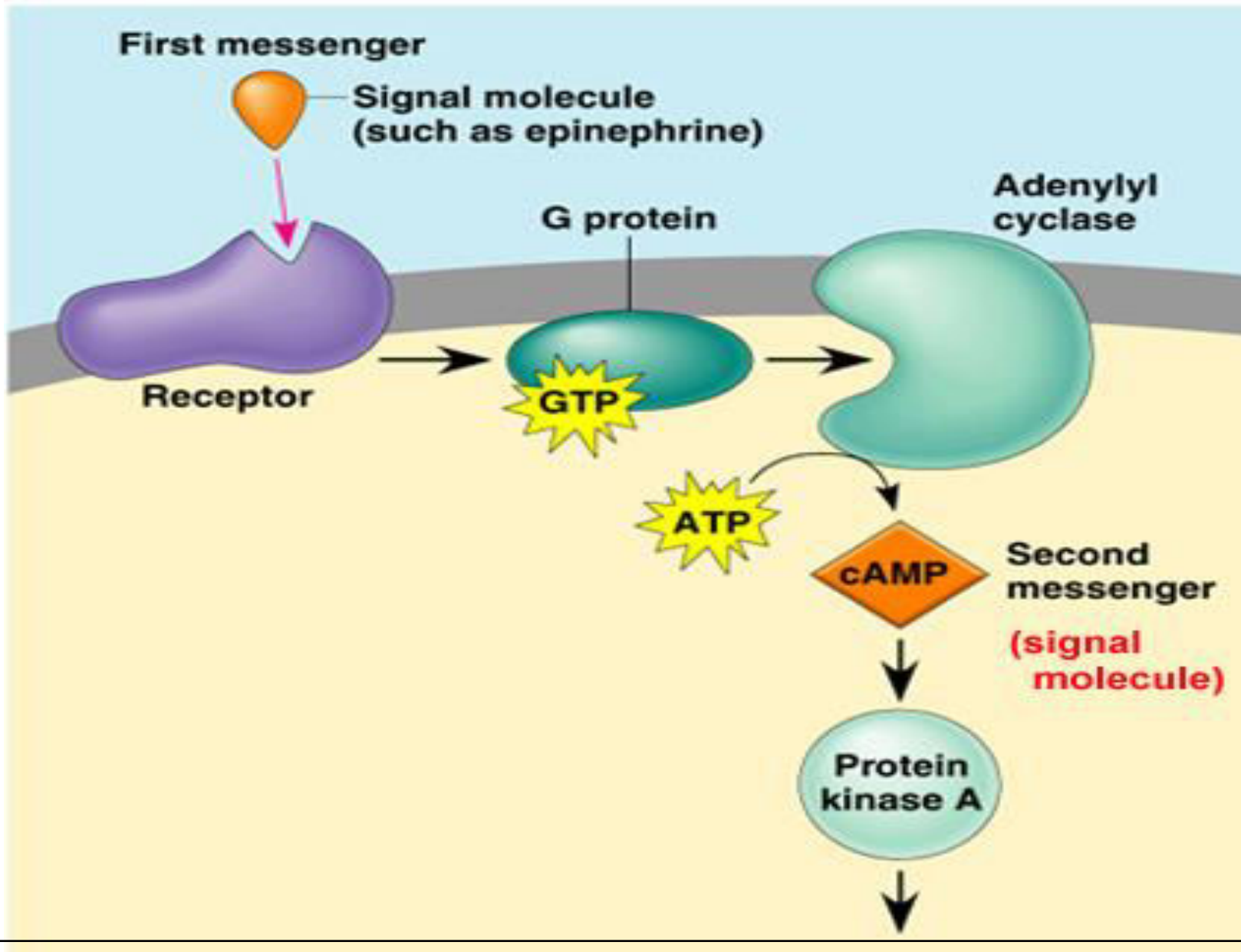
- Their main features is that the intracellular domain of the receptor is a kinase, that is activated when the messenger binds to the extracellular domain. Receptor kinase phosphorylates an amino acid residue that is present on the receptor or an associated protein.
- Message is transmitted through signal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

- **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 GTP into GDP 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.





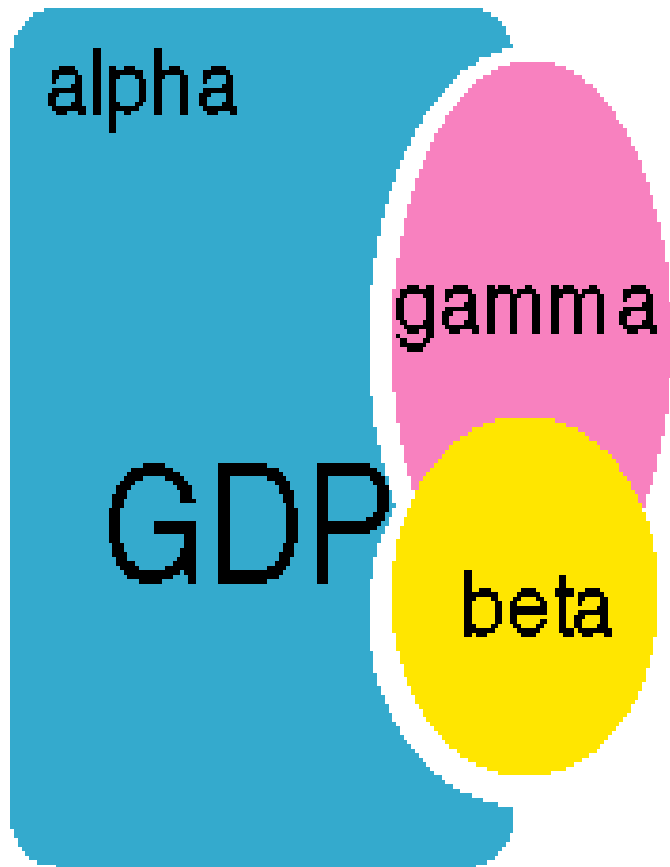


# G- protein receptors

## A. Basic G-protein Receptor

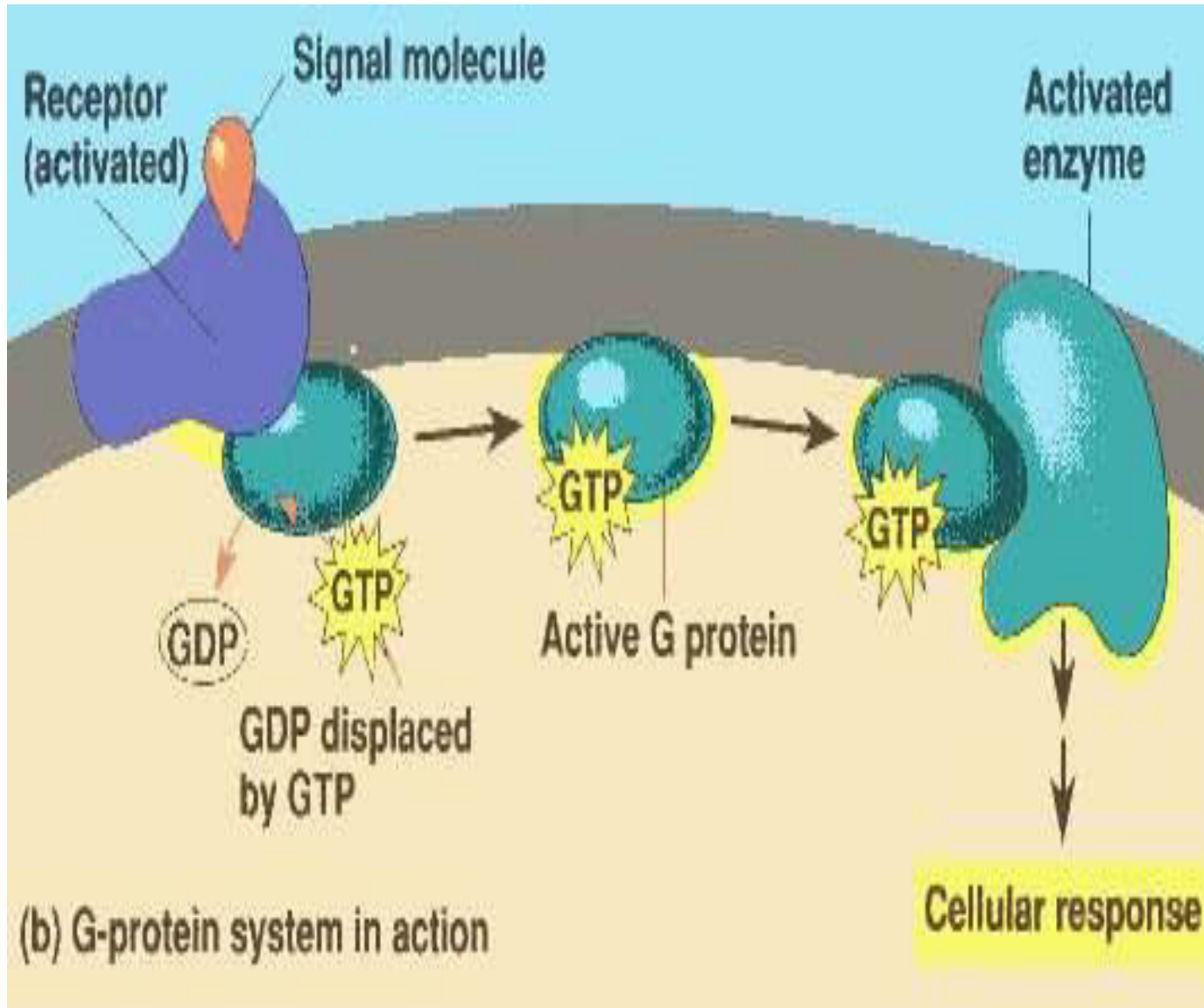
1. whole family of receptors
2. All use same basic pattern
  - a. **ligand binds** to receptor (outer surface of cell).
  - b. receptor **changes shape** (inner surface of cell).

- 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.



- 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** -R<sub>s</sub> or R<sub>i</sub>) and a regulatory complex ( **G**- G<sub>s</sub> or G<sub>i</sub>).




- **G-complex** is again composed of three subunits-  $\alpha$ ,  $\beta$  and  $\gamma$ .
- It is basically the  $\alpha$ -subunit that is either stimulatory or inhibitory.
- $\alpha$ -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  $\alpha$ -subunit and it dissociates from  $\beta$  and  $\gamma$  subunit.

- The  $\alpha$ s 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  $\alpha_s$  and  $\alpha_i-2$ .
- Due to which in  $\alpha_s$  intrinsic GTPase activity is disrupted and it cannot associate with its other subunits.
- In the  $\alpha_i-2$  dissociation is prevented, and  $\alpha_s$  activity is unopposed.

- 
- 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.