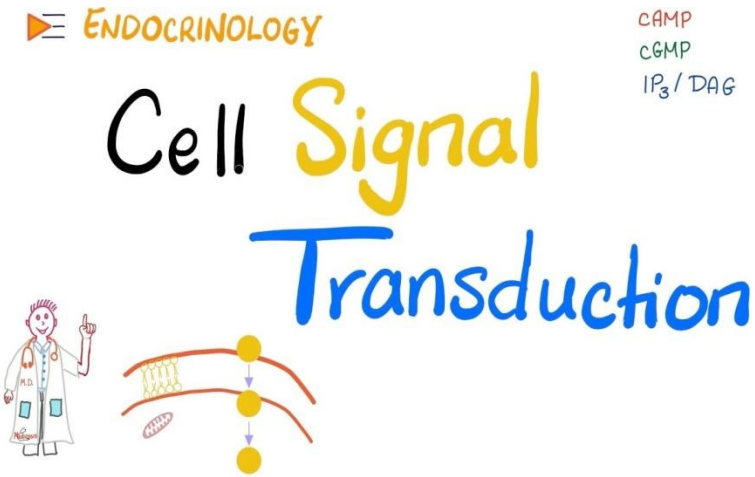
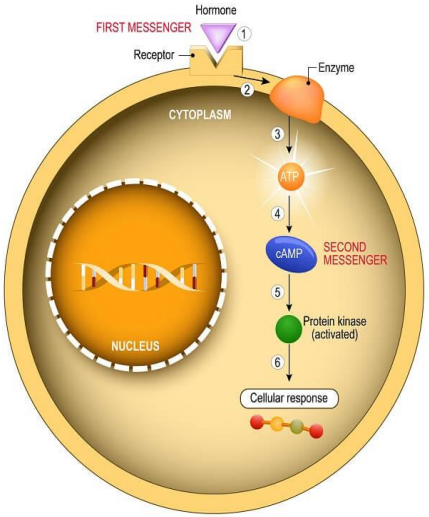
Mansoura National University
Faculty of Medicine

Level: 2

Semester: 3

Hormone Action & Signal Transduction





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Contents

- Introduction.
- Hormones and its classifications.
- Hormone receptors.
- Mechanism of hormone action.

Learning Outcomes (LOs)

At the end of this session, the students should be able to:

- Define hormones and recognize its classifications.
- Identify hormone receptors.
- Describe mechanism of hormone-receptor interactions and intracellular signal transduction components.
- Summarize the role of cAMP, cGMP, calcium , phosphatidyl inositol and tyrosine kinase as 2nd messengers.
- Correlate their knowledge to a clinical situation.

LO 1

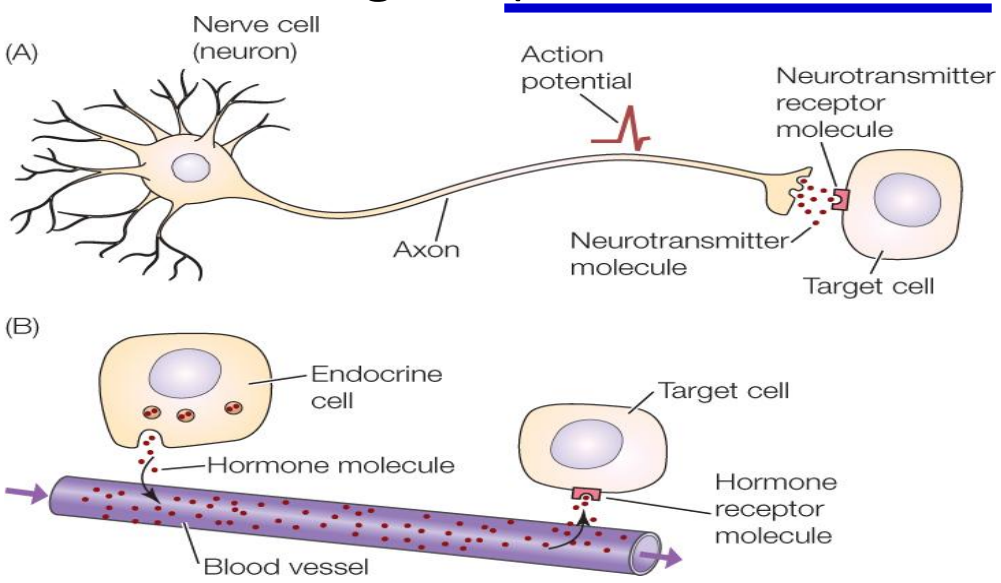
Define hormones and recognize its classifications

Introduction

❖ Survival of multi-cellular organisms depends on their ability to adapt to the constantly changing environment.

❖ Intercellular communication mechanisms are necessary for this adaptation.

❖ Nervous system and endocrine system provide this intercellular communication through chemical messengers (neurotransmitters and hormones, respectively).

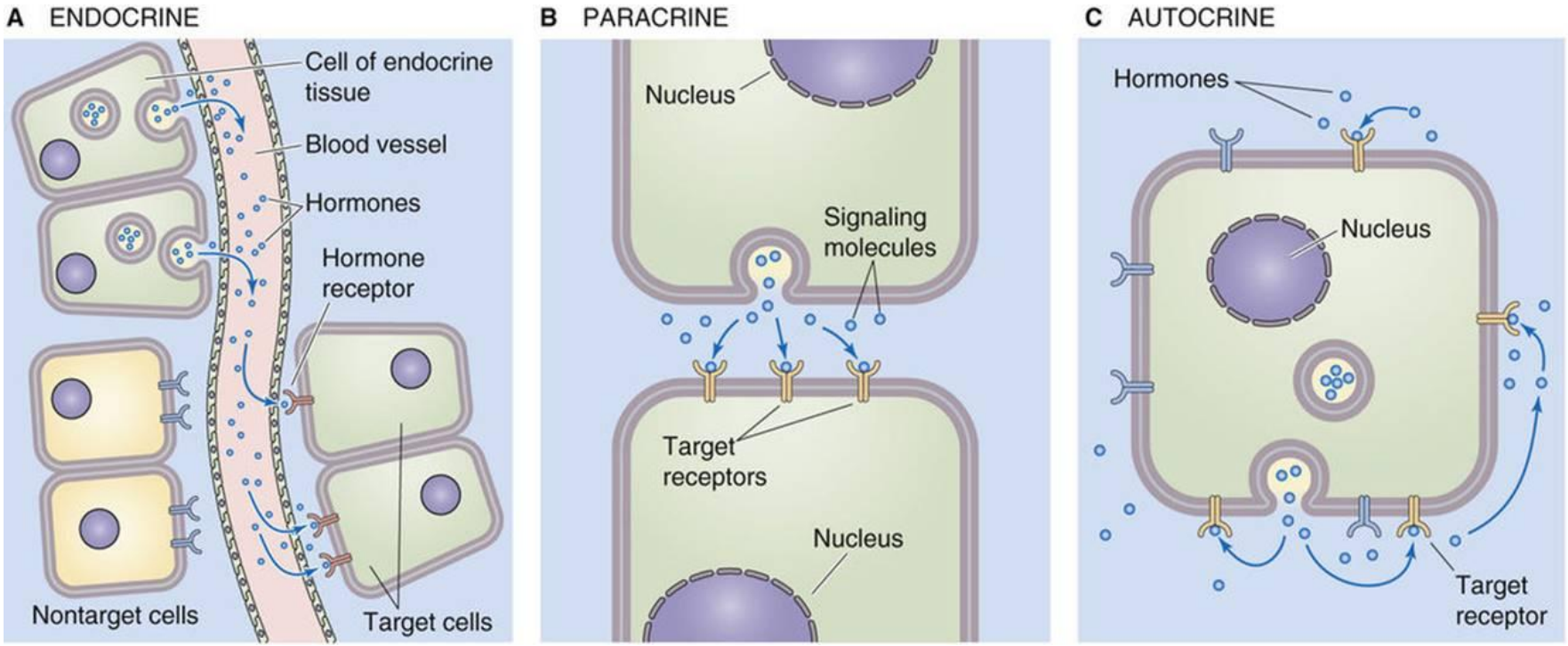


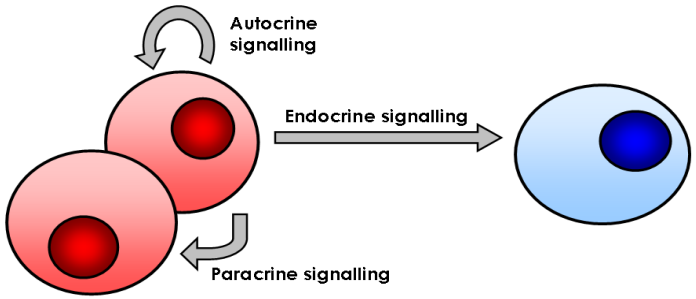
Introduction

4 Different signaling mechanisms

1. Endocrine signaling
2. Paracrine signaling
3. Synaptic signaling
4. Autocrine signaling

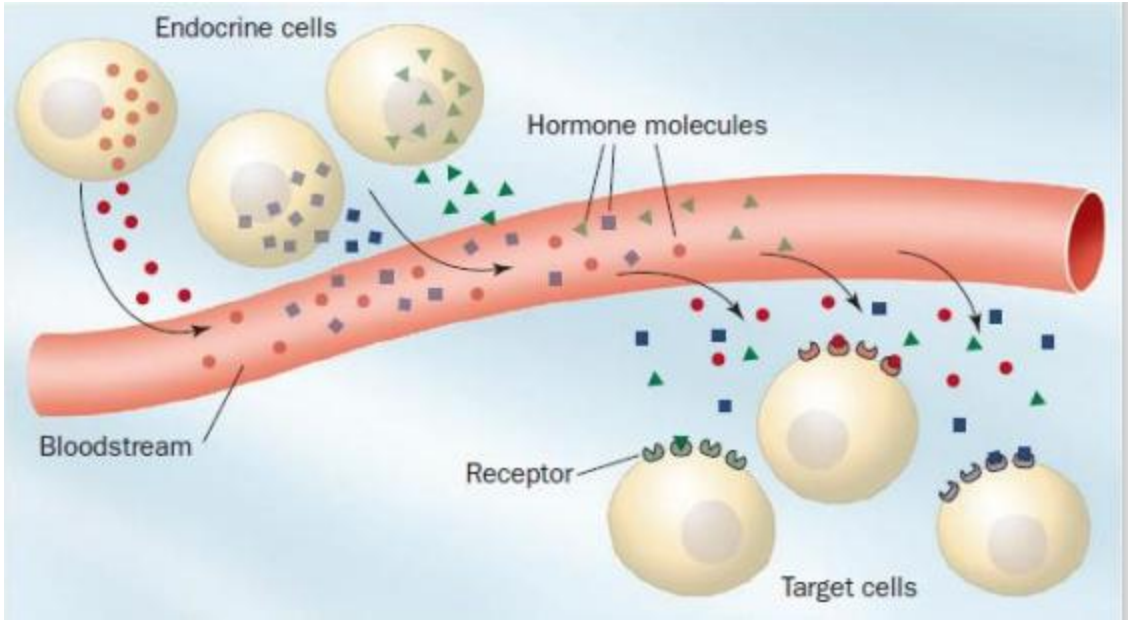
Introduction





Hormones

- They are signaling molecules (chemical messengers) synthesized and secreted from the endocrine glands.
- Hormones are released into the circulation to act on the **target cell**.



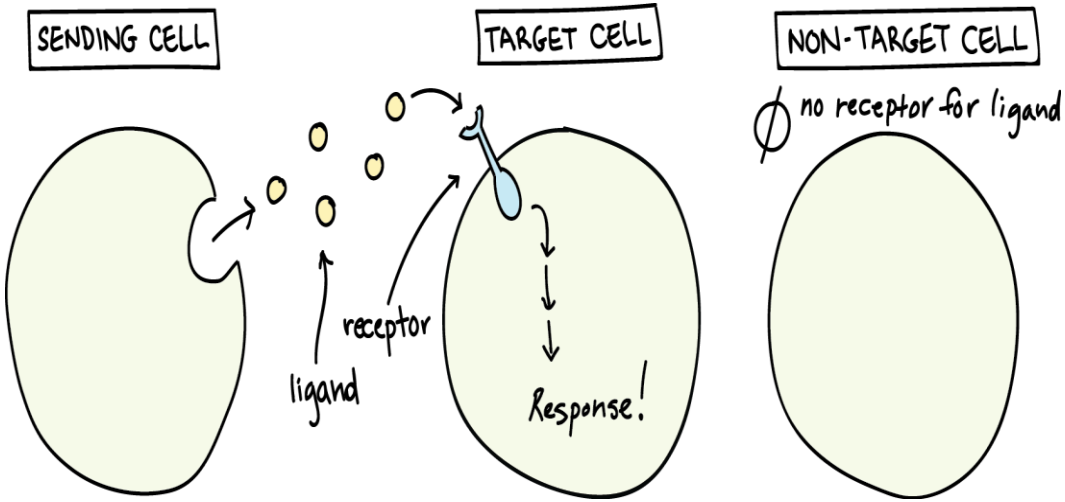
Hormones

- The target cell for the hormone (ligand) is **the cell that has the specific receptors for this hormone**.

Ligand-receptor interaction

Intacellular signaling

Response



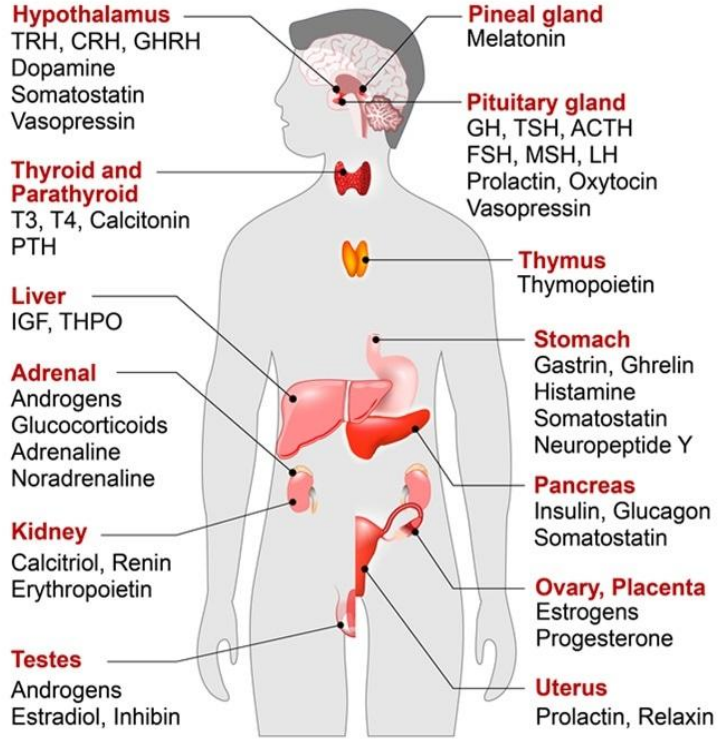
Hormones

➢ Classifications of hormones:

-Hormones can be classified according to the chemical nature, solubility, location of its receptors and the mechanism of hormone action.

1- acc to Chemical nature

2- acc to Mechanism of action



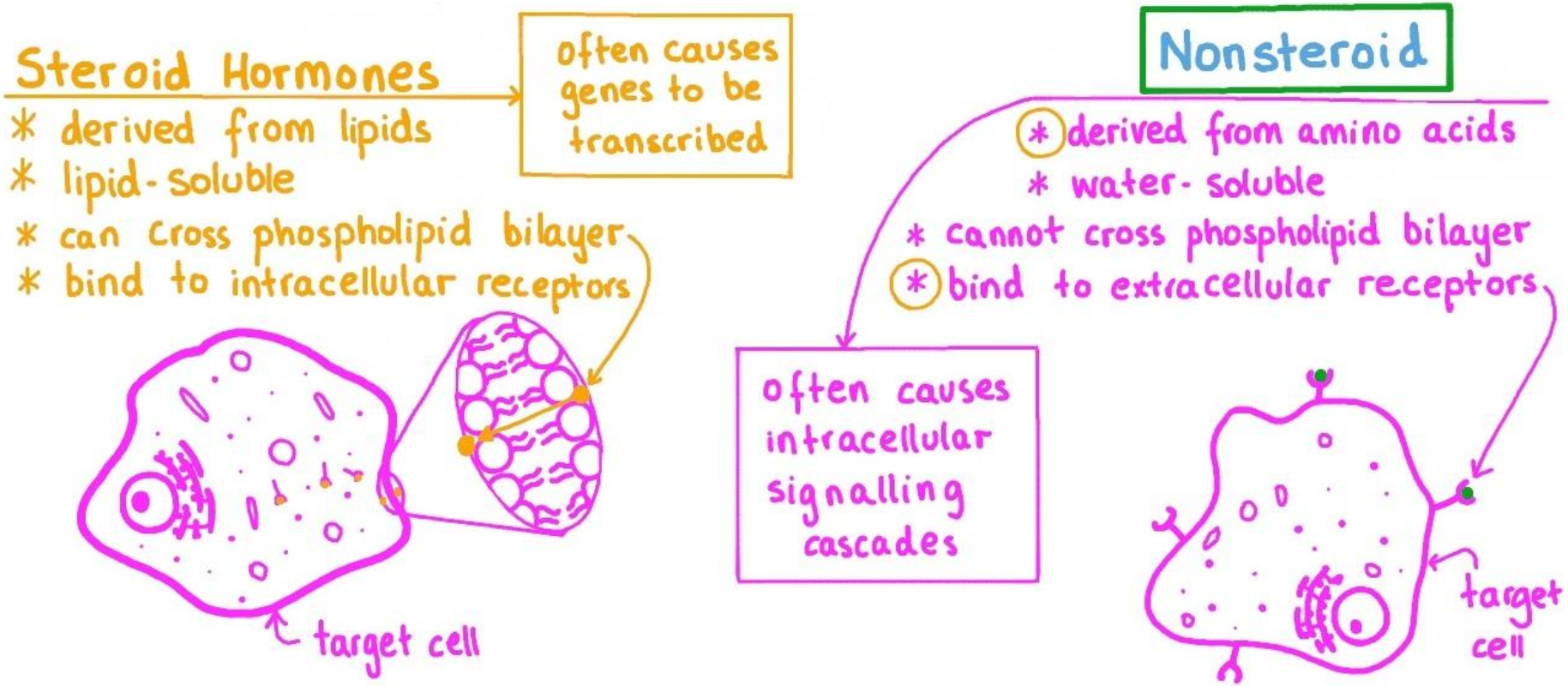
Hormones

1- acc to Chemical nature:

Steroid hormones	Non-steroid hormones
-They are derived from cholesterol. 1. Glucocorticoids 2. Mineralocorticoids 3. Sex hormones Androgens (testosterone) Estrogens progesterone	I. Protein Hormones: 1.Large polypeptides: -ex. Growth hormone – Insulin – Glucagon – Parathyroid hormone – Prolactin. 2.Small polypeptides: (small number of aa) -ex. ADH (9 aa) – Oxytocin (9 aa) – TRH (3 aa). 3.Glycoprotein hormones: -ex. FSH – LH – TSH – HCG. II. Amino Acid Derived Hormones: -These hormones are derived from aa. -ex. Thyroid hormones – Adrenaline – Noradrenaline – Dopamine from Tyrosine aa -ex. Melatonin from Tryptophan aa

Hormones

1- acc to Chemical nature:



Hormones

2- acc to Mechanism of action:

	Group I	Group II
Solubility	Fat soluble (lipophilic)	Water soluble (hydrophilic)
Transport in plasma	Bounded to plasma protein Long plasma half-life (hours to days)	Free (no need to bind plasma protein) Short plasma half-life (minutes)
Receptor	Intracellular	cell membrane
Mediator	Hormone itself bind to receptor on the DNA forming Hormone- Receptor complex	Second messenger
Mechanism of action	Binding with receptors in the nucleus→ Activate genes	Modifing the enzyme activity (phosphorylation→ ↑ or↓ enzym activity)
Response	Slower response, takes hours (Control of gene expression)	Fast response, takes minutes NB. Some act by controlling gene expression , so takes hours
Example	Steroid and thyroid hormones	Protein hormones & catecholamines

LO 2

Identify hormone receptors

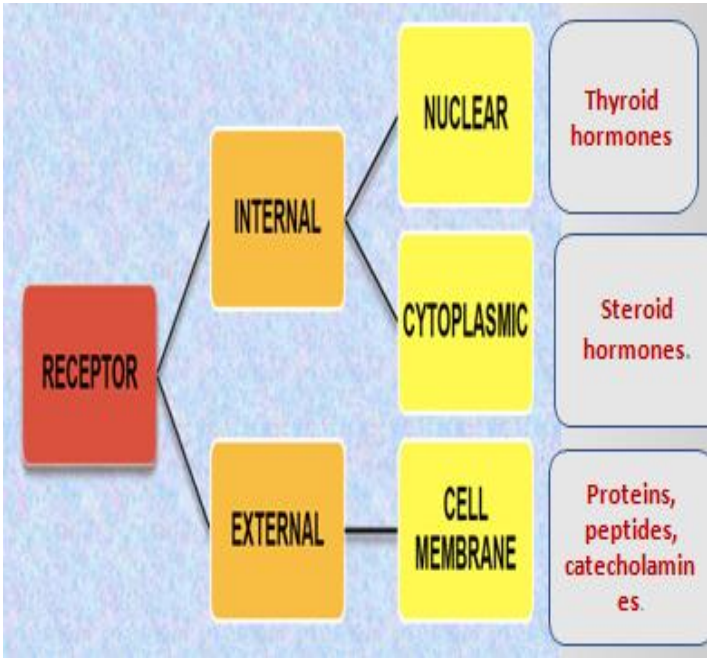
Hormone receptors

❖ They are:

✓ cell-associated **recognition molecules**.

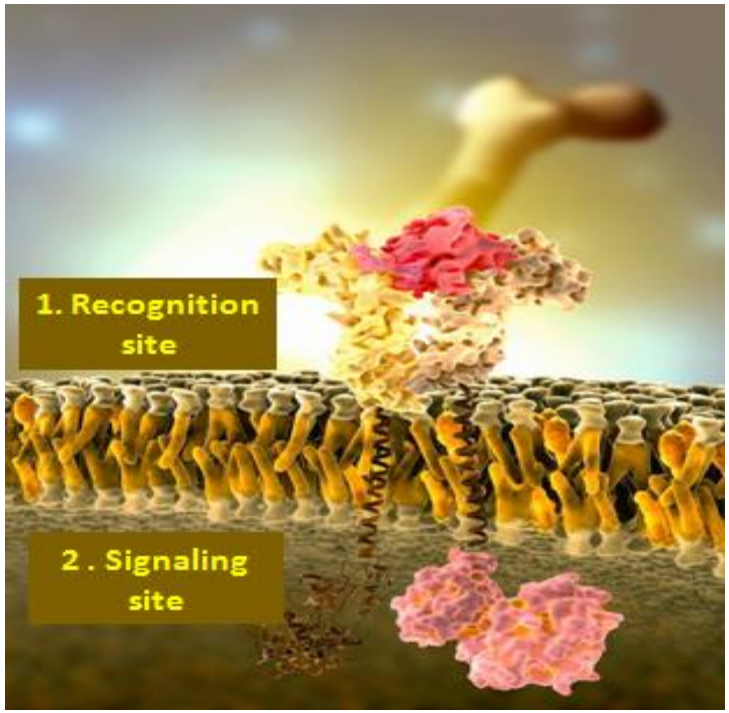
✓ **protein** in nature.

✓ located **inside the cell either in the cytosol or in the nucleus** (intracellular receptors) or located **in the plasma membrane** of the cell (cell-membrane receptors).



Hormone receptors

❖ Each receptor has two functional sites:



1. Recognition site:

It binds the hormone specifically.

2. Signaling site:

It couples hormone binding to intracellular effect.

LO 3 , 4

Describe mechanism of hormone-receptor interactions and intracellular signal transduction components

Summarize the role of cAMP, cGMP, calcium , phosphatidyl inositol and tyrosine kinase as 2nd messengers

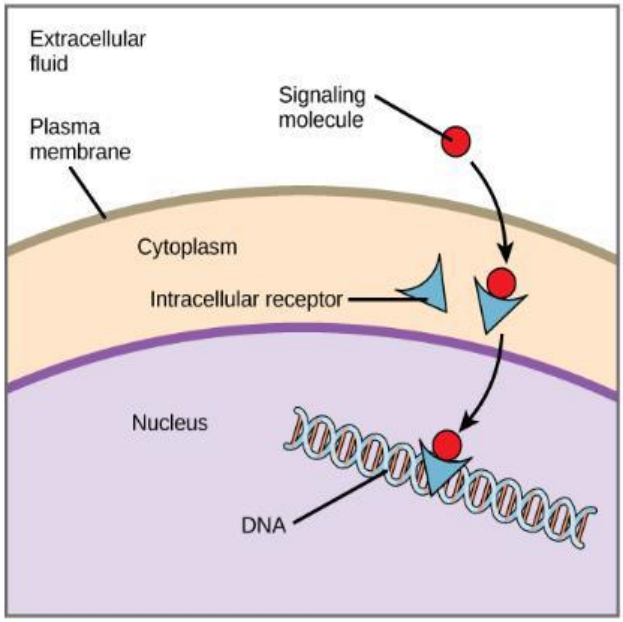
Mechanism of hormone action

Group I Hormones (bind to intracellular receptors)

Group II Hormones (bind to membrane receptors)

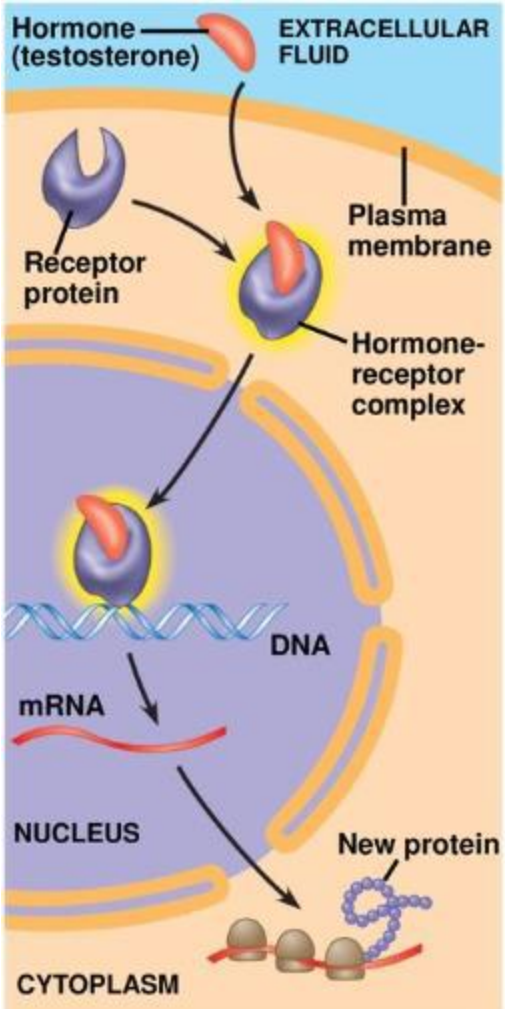
Mechanism of action of Group I Hormones

- The lipophilic group I hormones are transported in blood bounded to plasma proteins.
- They diffuse through the plasma membrane of cells, bind their specific, high-affinity intracellular receptors in target cells, forming **hormone-receptor complex.**
- These receptors can be located in the **nucleus** or in the **cytoplasm** (then the hormone-receptor complex traverses the nuclear membrane) of target cells.

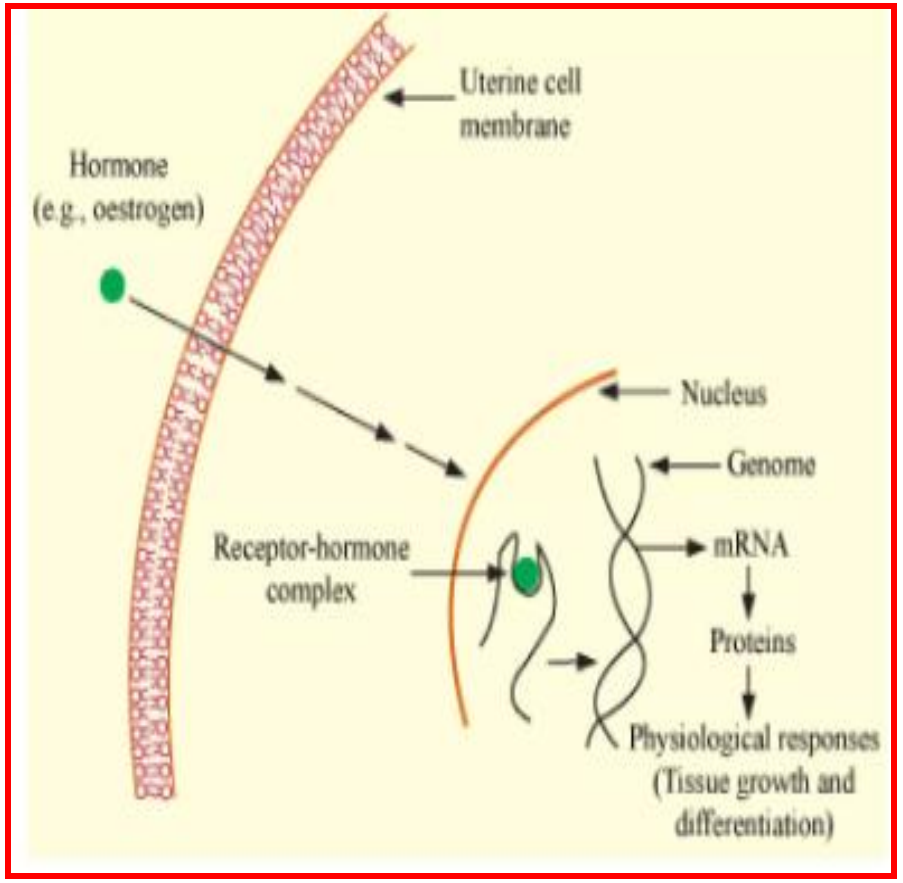


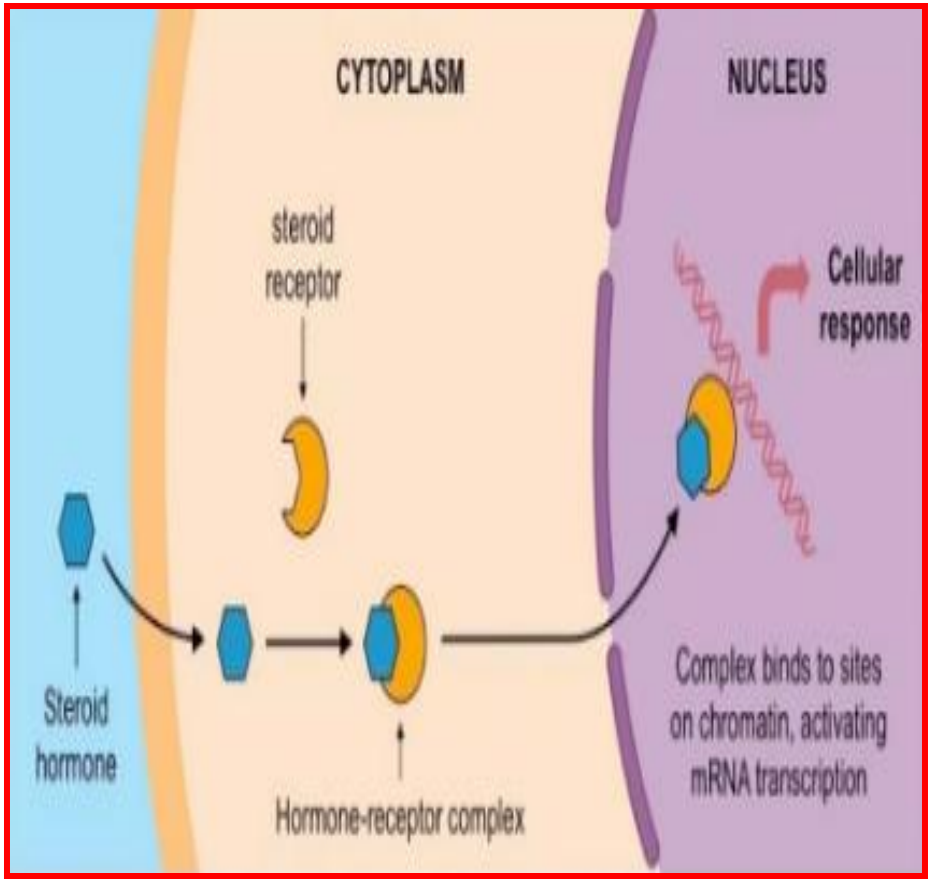
Mechanism of action of Group I Hormones

- The activated **hormone receptor complex** binds with high affinity to a specific DNA sequence called the **hormone response element (HRE).**
- This results in recruitment of RNA polymerase II and the GTFs and activation of gene transcription.
- Transcription of DNA into mRNA→ mRNA leaves the nucleus→ attaches to a ribosome in cytoplasm → directs the synthesis of a specific protein product (translation).



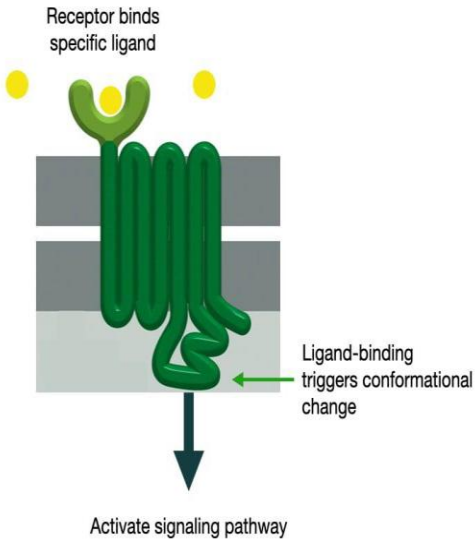
Mechanism of action of Group I Hormones





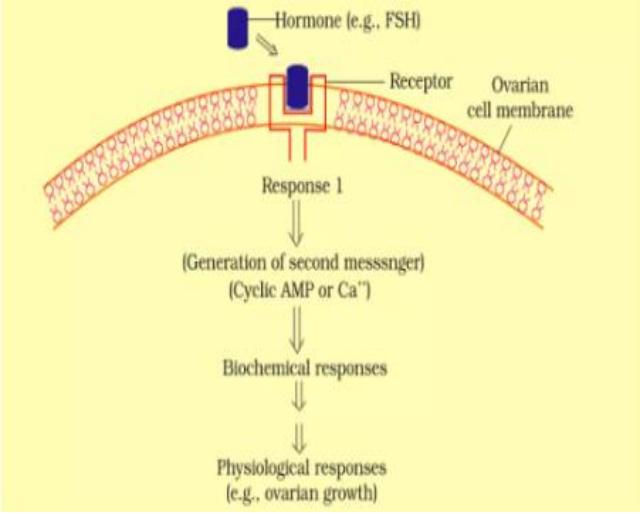
Mechanism of action of Group II Hormones

- The water soluble hormones (hydrophilic) have no transport proteins and can not freely cross the plasma membrane.
- They initiate a response by binding to a receptor located in **the plasma membrane**.
- The receptor complex activates series of intracellular molecules called **second messengers**, which initiate cell activity.
- This process is called signal transduction, because the external signal (hormone) is transduced via internal intermediates.



Mechanism of action of Group II Hormones

➢ **The second messenger** is the signal produced as a result of hormone binding to its cell membrane receptor, mediating the effects of the hydrophilic hormones.



Q who is the first messenger??

⟶ Hormone.

➢ **Second messengers may be:**

1) Cyclic Adenosine Monophosphate **(cAMP)**.
2) Cyclic Guanosine Monophosphate **(cGMP)**.
3) **Calcium or phosphatidyl inositides (PIs) or both**.
4) **Protein kinase** cascade.

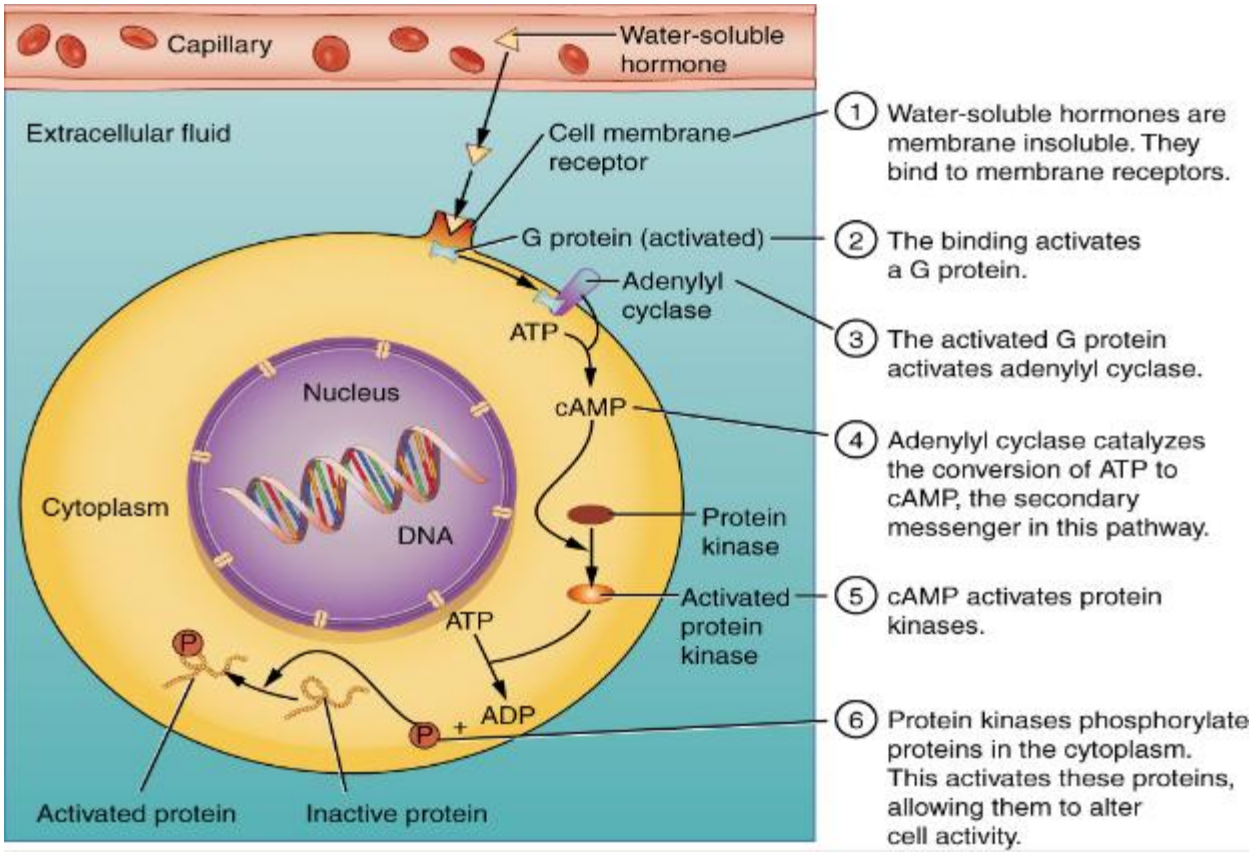
Cyclic AMP as a 2nd messenger

- **Examples of hormones use cAMP as a second messengers:**

✓ **Catecholamines.**

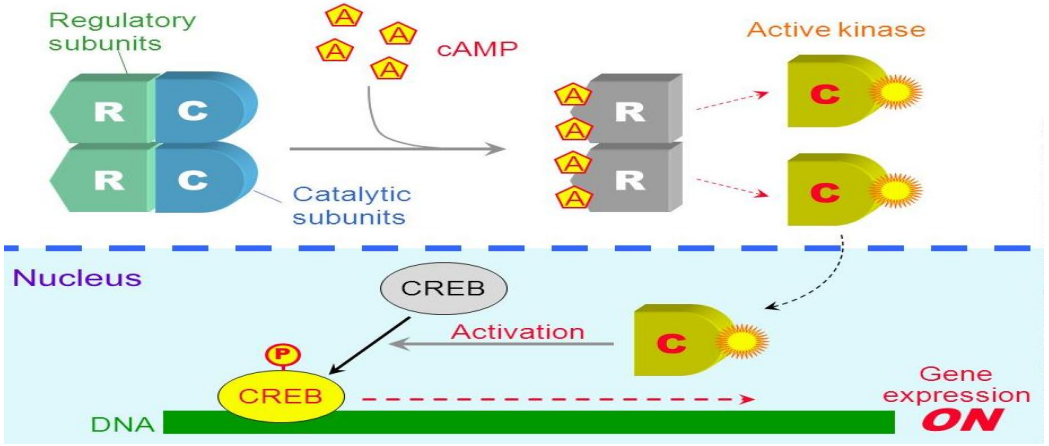
✓ **Calcitonin.**

✓ **FSH, ACTH, TSH, PTH.**



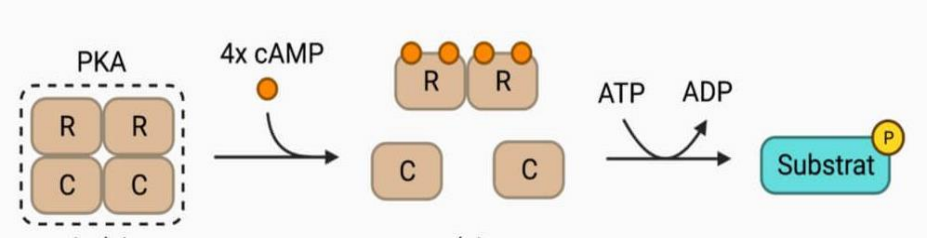
Cyclic AMP as a 2nd messenger

- Binding of the hormone (ligand) to cell membrane receptor→ activates a **regulatory G protein (Gs)**→ activates adenylate cyclase enzyme→ catalyzes the formation of cAMP from ATP.
- Then **cAMP**:
  a) Activates **protein kinase A (PKA)** →Phosphorylation of certain enzymes
  Or b) Bind to DNA sequence → **Control Gene Expression**.



Cyclic AMP as a 2nd messenger

- PKA exists in an inactive form as an **R2C2 heterotetramer** consisting of **two regulatory (R) and two catalytic (C) subunits**.
- The cAMP binds to the regulatory subunit of PKA. This results in dissociation of the regulatory and catalytic subunits and activation of the catalytic subunits.



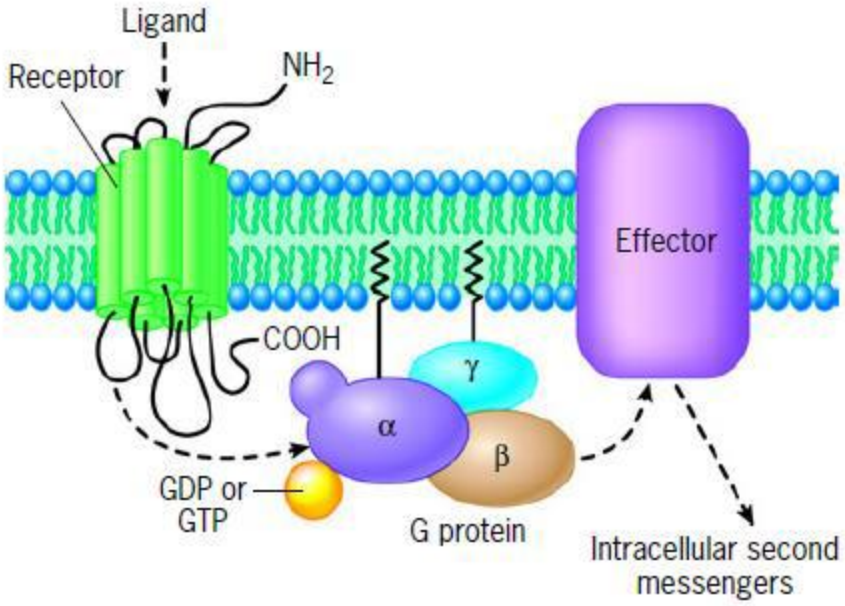
- **Termination of hormone action:**

  → **phosphodiesterase enzyme (PDE)** hydrolyses cAMP to AMP, and stop its action.

NB. Some hormones act via inhibition (not activation) of adenyl cyclase.

G-regulatory protein

- A GTP-binding protein is a regulatory protein, consists of 3 polypeptide subunits (trimeric):
  - → **α subunit.**
  - → **β subunit.**
  - → **γ subunit.**

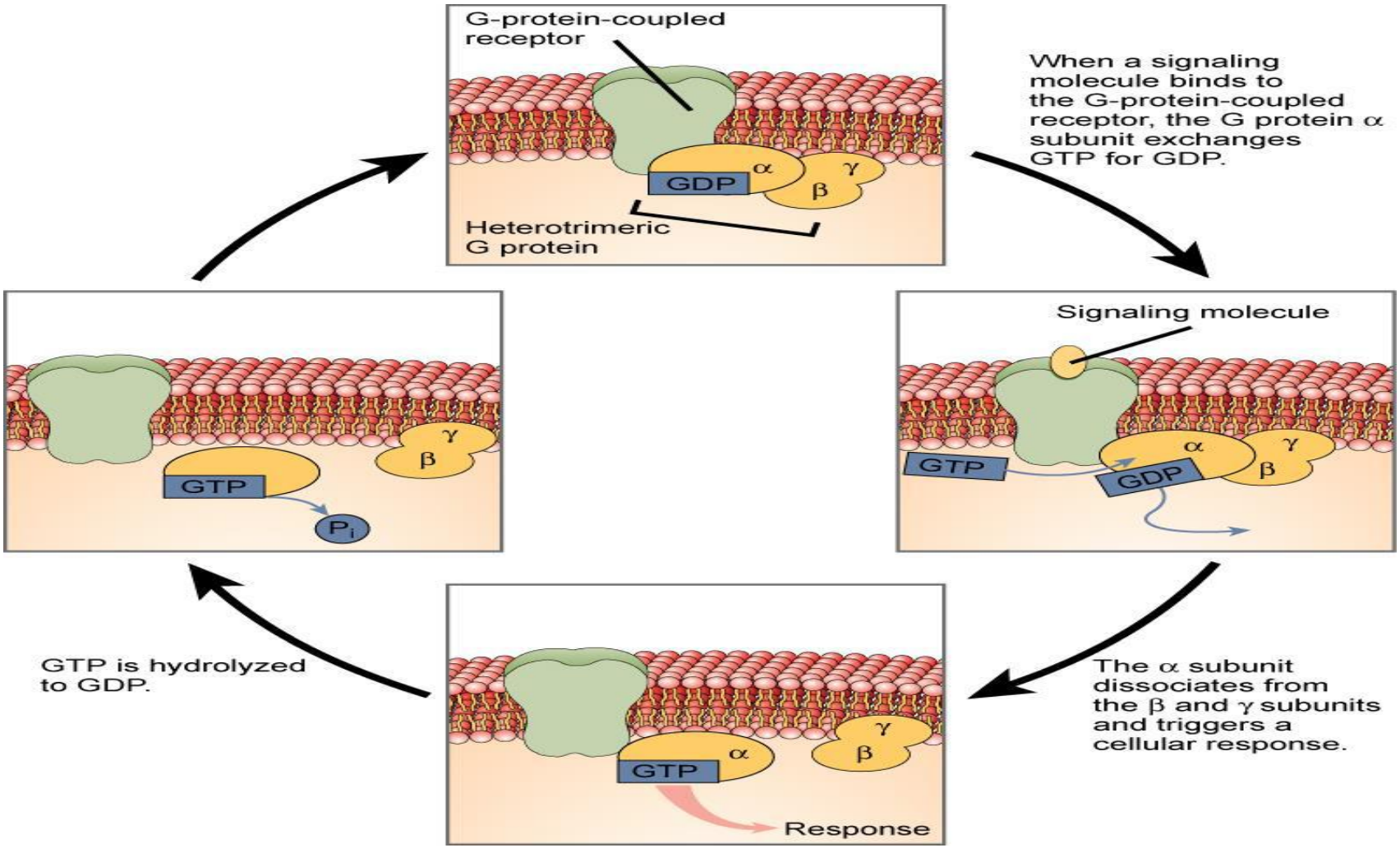


NB. **α subunit: is responsible for the activity of the G protein**, binds GDP and GTP, hydrolyzes GTP, and activates adenylate cyclase.

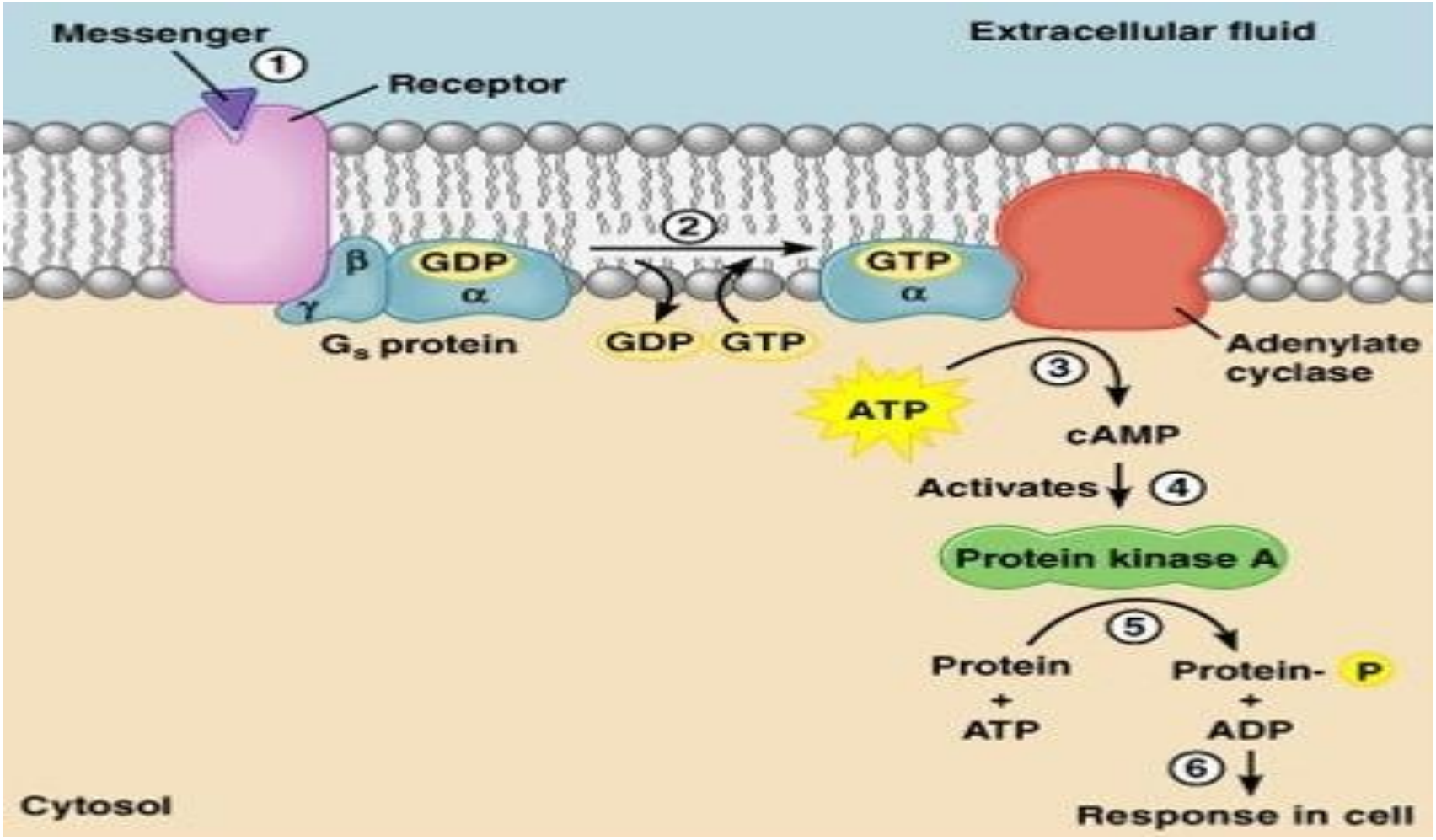
G-regulatory protein

- Binding of the hormone to its receptor activates G protein.
- G α subunit releases its GDP and binds GTP.
- There are several types of G proteins:
  - **Gs:** Stimulates adenylate cyclase.
  - **Gi:** Inhibits adenylate cyclase.
  - **Gq:** Stimulates phospholipase C.
  - **Other types affect Ca channels and K channels.**

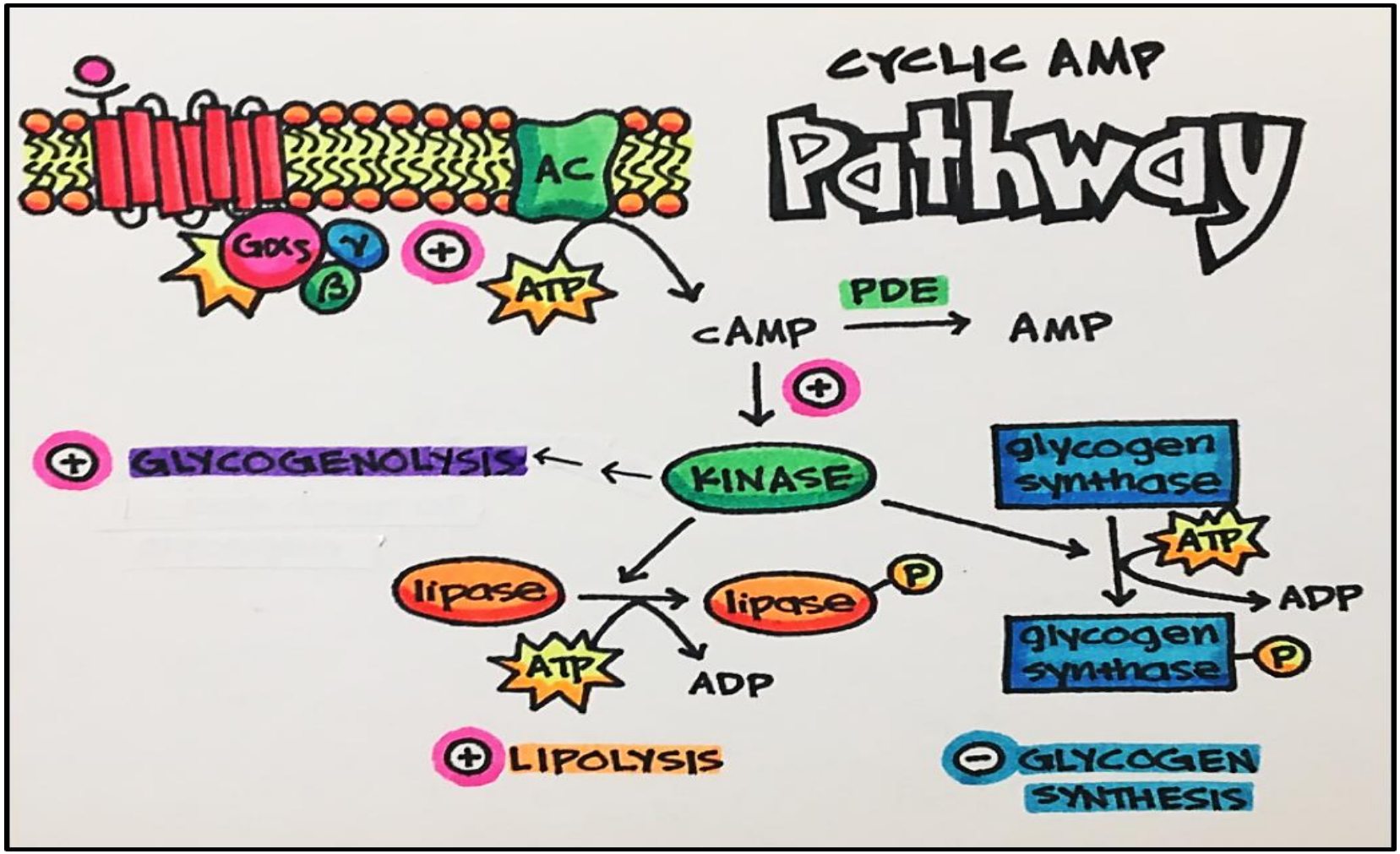
G-regulatory protein



Cyclic AMP as a 2nd messenger



Cyclic AMP as a 2nd messenger



Cyclic GMP as a 2nd messenger

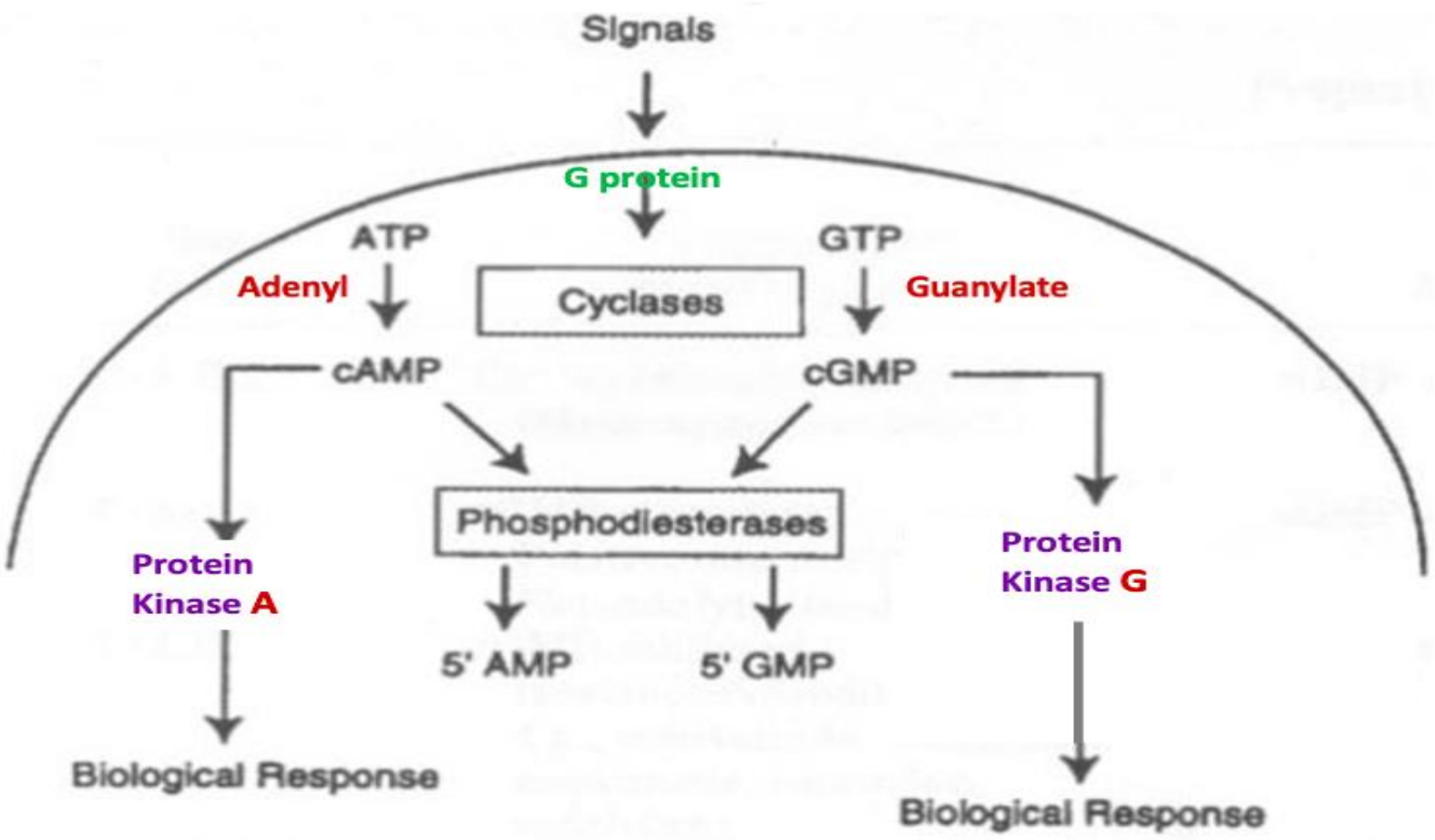
✓ **Examples of hormones use cGMP as a second messengers:**

Atrial natriuretic factor (ANF).

✓ Binding of hormone to its specific receptor→ activates the **membrane bound form of guanylate cyclase** → catalyzes the transformation of GTP to cGMP→ **cGMP activates protein kinase G (PKG)** → protein phosphorylation→ mediate the effects of the hormone (**ANF: smooth muscle relaxation, vasodilatation**).

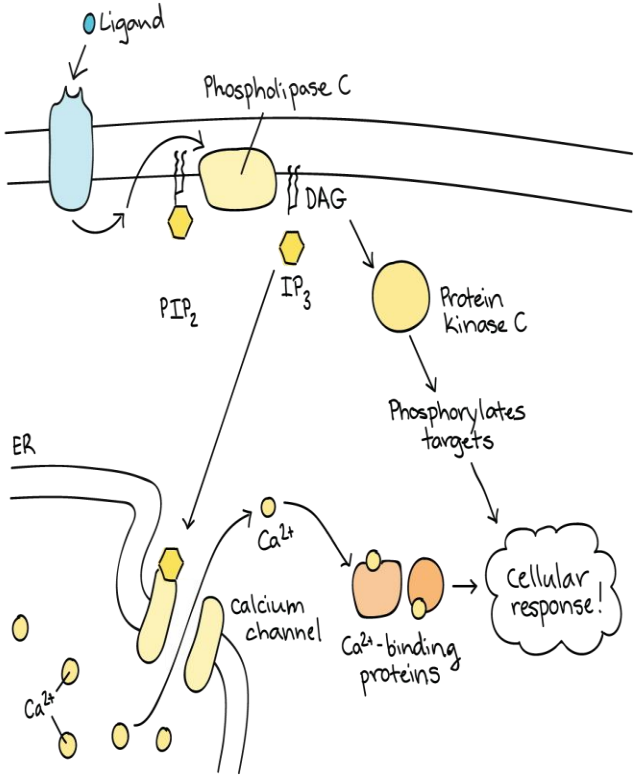
✓ After mediating its effects, cGMP is hydrolyzed by **cGMP dependent PDE enzyme** to 5' GMP.

cAMP and cGMP as a 2nd messenger



Calcium or phosphatidyl inositides (PIs) as a 2nd messenger

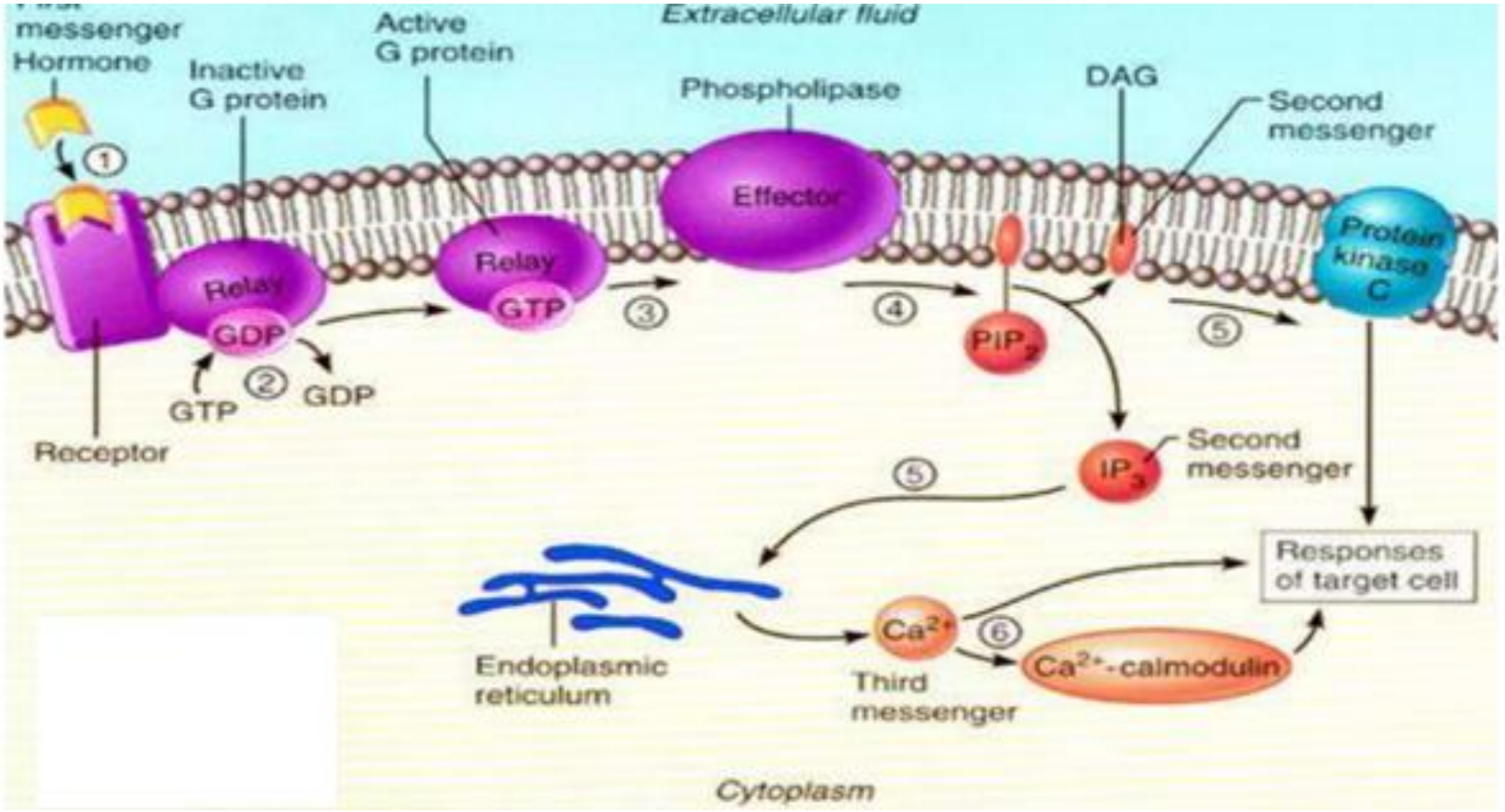
- ✓ **Examples of hormones use Ca or PIs as second messengers:** **Angiotensin II, ADH, TRH.**
- ✓ Binding of the hormone (ligand) to its specific receptor → **activates G protein (Gq)** → activates the **phospholipase C (PLC)** enzyme → The active PLC hydrolyses phosphatidyl inositol biphosphate (PIP2) to: **DAG and IP3**.



Calcium or phosphatidyl inositides (PIs) as a 2nd messenger

- ✓ **Diacyl glycerol (DAG)**→ activates **protein kinase C (PKC)**→ phosphorylates of enzymes/protein → mediate the effects of the hormone.
- ✓ **Inositol Triphosphate (IP3)**→ bind to Ca Channel→ releases Ca2+ from intracellular storage sites (ER , Mitochondria) → Ca2+ binds to Ca binding protein (calmodulin) to form Ca2+/ calmodulin complex→ phosphorylation of enzymes → mediate the effects of the hormone.

Calcium or phosphatidyl inositides (PIs) as a 2nd messenger



Tyrosine (Protein) kinase as a 2nd messenger

- **<u>Examples of hormones use tyrosine kinase as a second messengers:</u> GH, Insulin.**
- Tyrosine kinases may be:
  a) Intrinsic part of the receptor **(ex. Insulin).**
  b) Intracellular associated with the receptor but not an intrinsic part of it **(ex. GH).**

Tyrosine (Protein) kinase as a 2nd messenger

Insulin binds to its receptor

↓

Autophosphorylation Tyrosine Kinase part of the receptors

↓

Activation of **IRS** (insulin receptor substrate)

↙ ↘

PI3 kinase — **RAS, RAF, MAP cascade**

↓ ↓

Mediate the effect of insulin

Growth hormone binds to its receptor

↓

Activation of Associated Tyrosine Kinase
JAK (Jauns Kinases) or **TYK** (Tyrosine Kinases).

↓

Activation of **STAT** (Transducers and Activators of Transcription protein)

↓

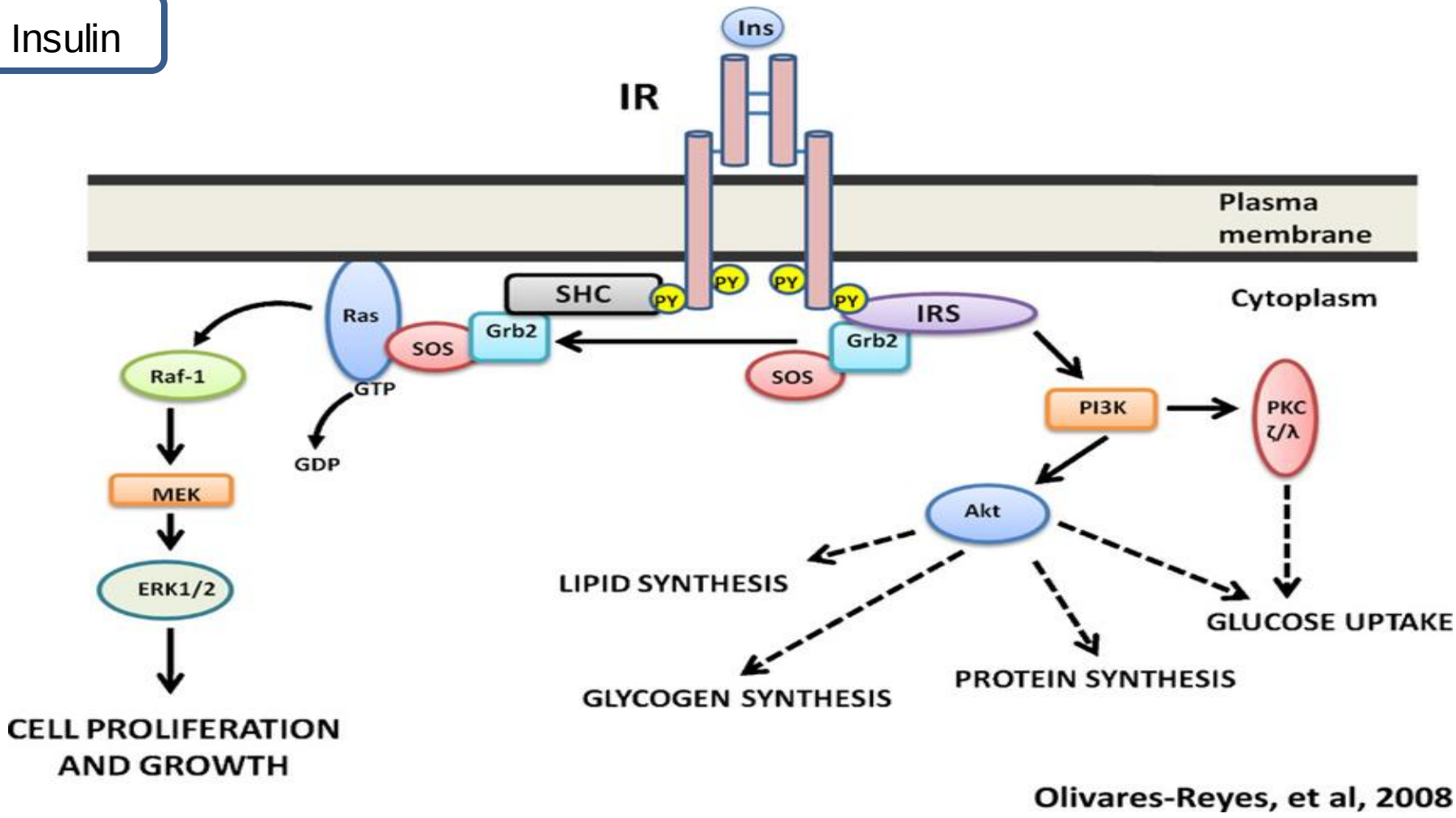
Move from cytoplasm to the nucleus, **bind specific DNA**

↓

Activate transcription

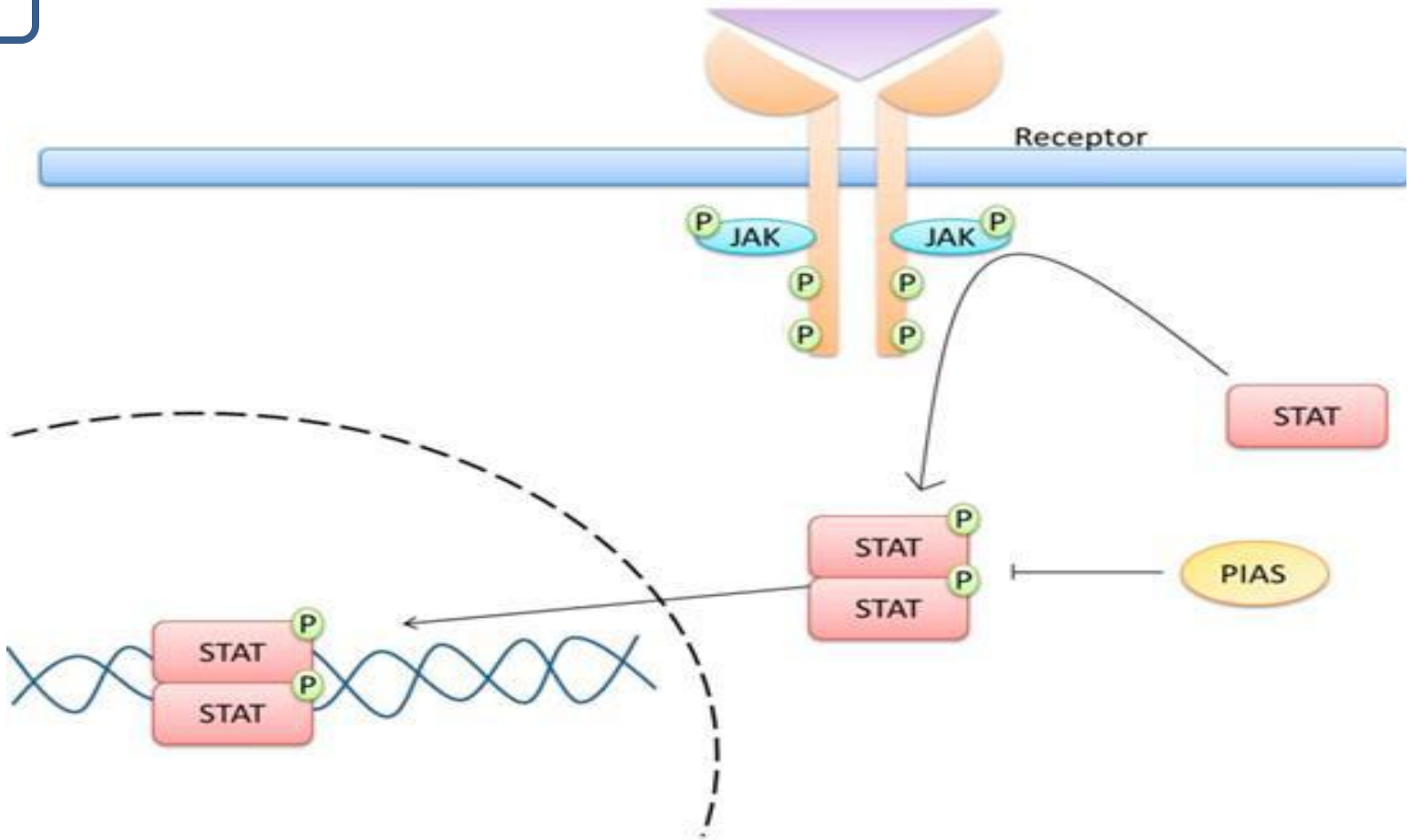
Tyrosine (Protein) kinase as a 2nd messenger

Insulin



Tyrosine (Protein) kinase as a 2nd messenger

GH



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Thank
You