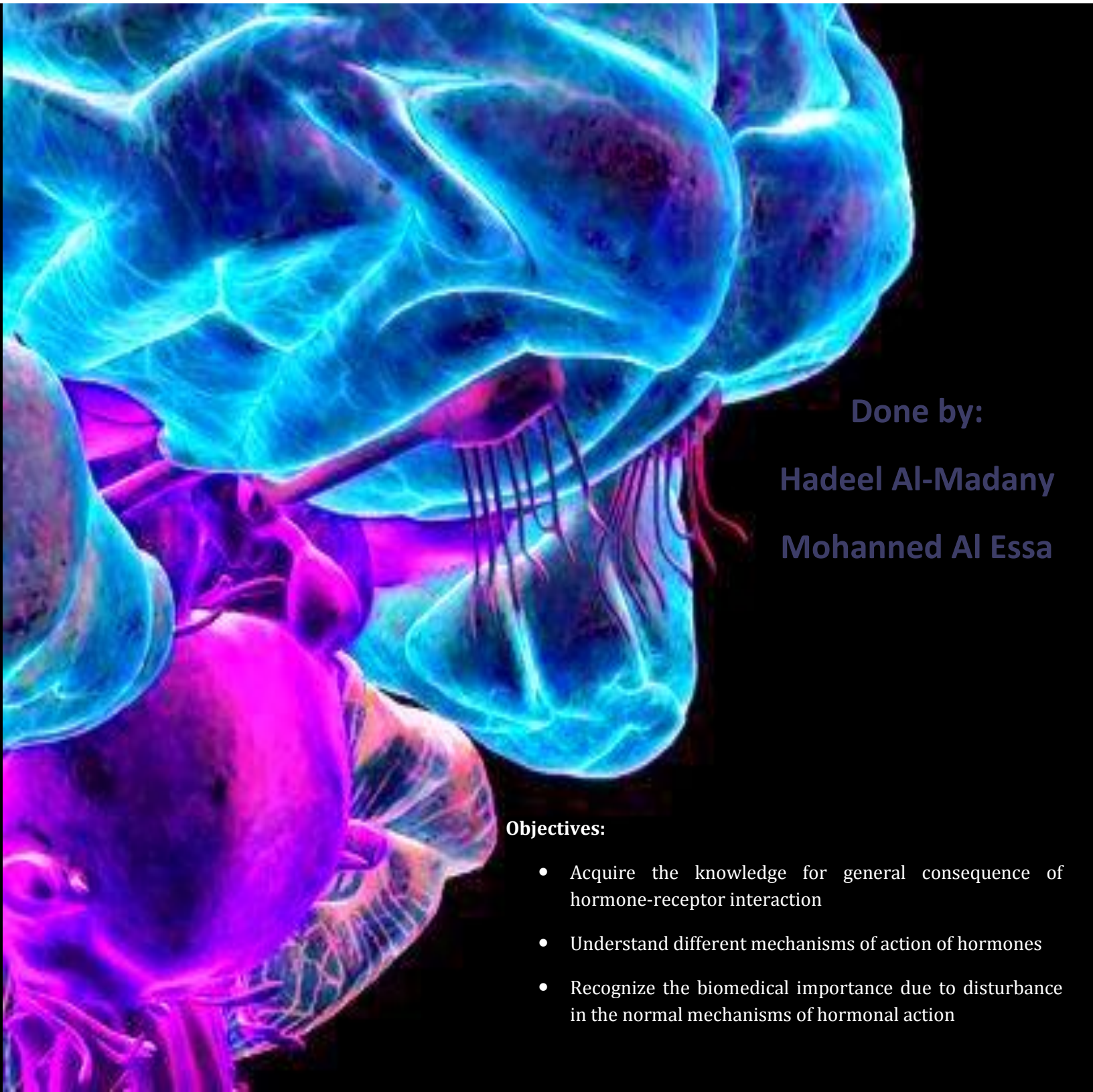


General mechanisms of hormone action



Done by:

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Mohanned Al Essa

Objectives:

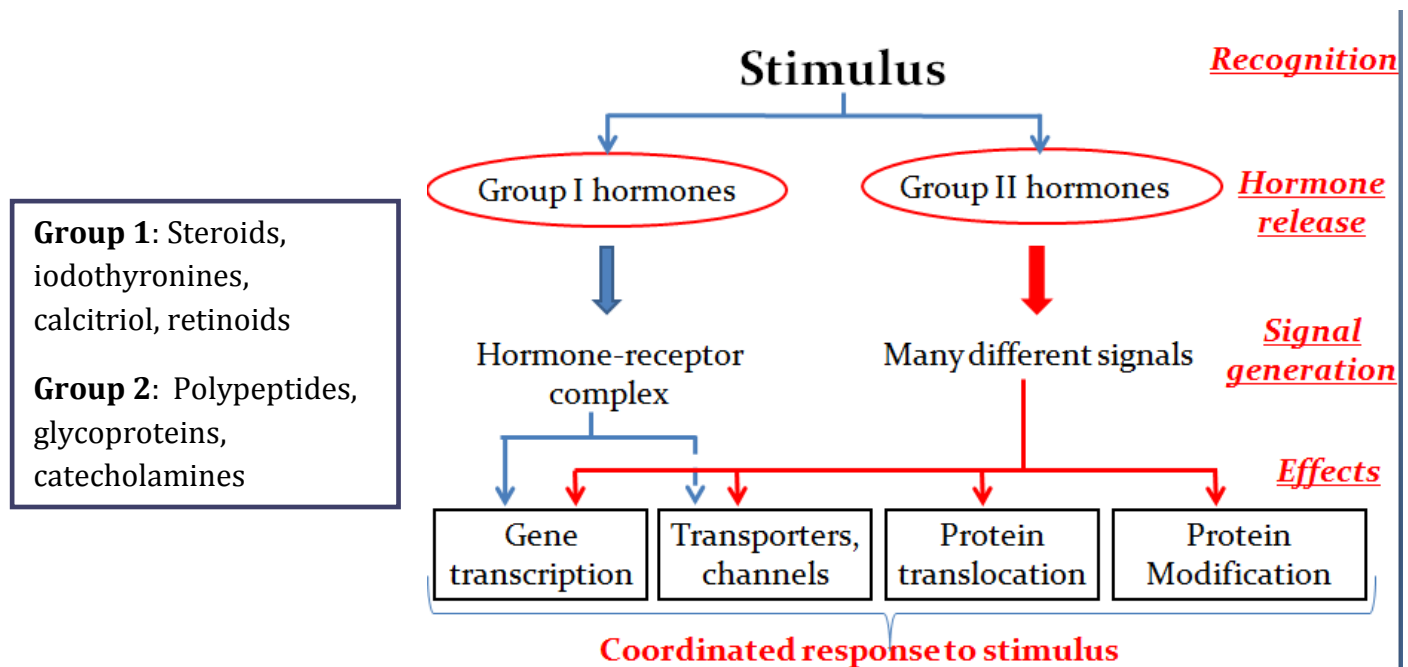
- Acquire the knowledge for general consequence of hormone-receptor interaction
- Understand different mechanisms of action of hormones
- Recognize the biomedical importance due to disturbance in the normal mechanisms of hormonal action

Background

- Hormone is a substance that is secreted from an endocrine gland to work upon a specific receptor.
- These receptors are either located:
 - On the plasma membrane (with hydrophilic hormones)= **proteins**
 - Intracellular (with hydrophobic hormones)= **steroids**
- The effects of these hormones are done with the help of signaling pathways “messengers”.
- Multicellular organisms depend in their survival on their adaptation to a constantly changing environment (If the environment around the cell was normal it doesn't need adaptation, but if it was changing it will adapt to cope with these changes. The process of adaptation occurs by secreting specific hormones)
- Intercellular communication is necessary for this adaptation to take place
- Human body synthesizes many hormones that can act specifically on different cells of the body
 - After meal → **Insulin** is the upper hand hormone (↓ glucose level).
 - Fasting → **Glucagon** is the upper hand hormone (↑ glucose level).
- More than one hormone can affect a given cell type
- Hormones can exert many different effects in one cell or in different cells
- A target is any cell in which the hormone (ligand) binds to its receptor

Factors determining the response of a target cell to a hormone:

- The rate of synthesis & secretion of the hormones
- The conversion of inactive forms of the hormone into the fully active form
 - Many hormones are secreted as prepro- or pro- hormones → activated by converting it to hormone. (E.g. Parathyroid Hormone (PTH) is secreted as Prepro- → Pro- → Activated hormone).
- The rate of hormone clearance from plasma (half-life & excretion)
 - **Long half-life:** Stays in the plasma for a long time. **Could be hours to days.**
 - **Short half-life:** Stays in the plasma for a short time. **Only minutes.**
- The number, relative activity, and state of occupancy of the specific receptors
 - This includes the Up and Down regulation of receptors
- Post receptor factors



There might be signal overlapping meaning that a hormone from **group two** which are catecholamines and poly-peptides can make more than one effect, and those effects combine together to give a response. This response may affect the gene transcription level, translation, transporters, modification.

Group I Hormones: The hormone receptor complex act as a second messenger.

Group II Hormones: Sends a second messenger

General Features of Hormone Classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-life	<ul style="list-style-type: none"> Long (hours – days) carried by plasma proteins (Prealbumin, Albiminm Globulin) and thus it has a long half-life. 	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex (the active form)	cAMP, cGMP, Ca ²⁺ , metabolites of complex phosphoinositols, tyrosine kinase cascades

Classification of Hormones by Mechanism of Action

Hormones that bind to intracellular receptors (Steroid-Thyroid superfamily) :

- Steroid hormones
- Thyroid Hormones (T_3 & T_4)
- Calcitriol ($1,25[OH]_2-D_3$)
- Retinoic acid

Hormones that bind to cell surface receptors

- A hormone may have more than one mechanism of action (Catecholamines), this means that a hormone can work on more than one receptor.
- ADH has two receptors:
V1 → Extrarenal.
V2 → Inside the renal tissue (Collecting Ducts) to help in reabsorption of water.
- **Calcitonin** is secreted from thyroid (C Cells of Thyroid).

A. The second messenger is cAMP:

- Catecholamines (α_2 - Adrenergic)
- Catecholamines (β - Adrenergic)
- Ant. Pituitary: ACTH, FSH, LH & TSH
- ADH (Renal V2-receptor)
- Calcitonin & PTH
- Glucagon

B. The second messenger is cGMP

- Atrial natriuretic peptide (ANP)
- Nitric oxide

C. The second messenger is Calcium or phosphatidylinositol (IP_3) (or both)

- Acetylcholine (muscarinic)
- Catecholamines (α_1 - Adrenergic)
- Angiotensin II
- ADH (vasopressin): Extra-renal V1-receptor

Vasopressin works on **V1** (Extrarenal ADH receptor).

D. The second messenger is a tyrosine kinase cascade

- GH & Prolactin
- Insulin
- Erythropoietin

Group I. Hormones that bind to intracellular receptors

✓ Steroid Hormones:

- Glucocorticoids
- Mineralocorticoids
- Sex hormones:
 - Male sex hormones: Androgens
 - Female sex hormones: Estrogens & Progestins

✓ Thyroid Hormones (T_3 & T_4)

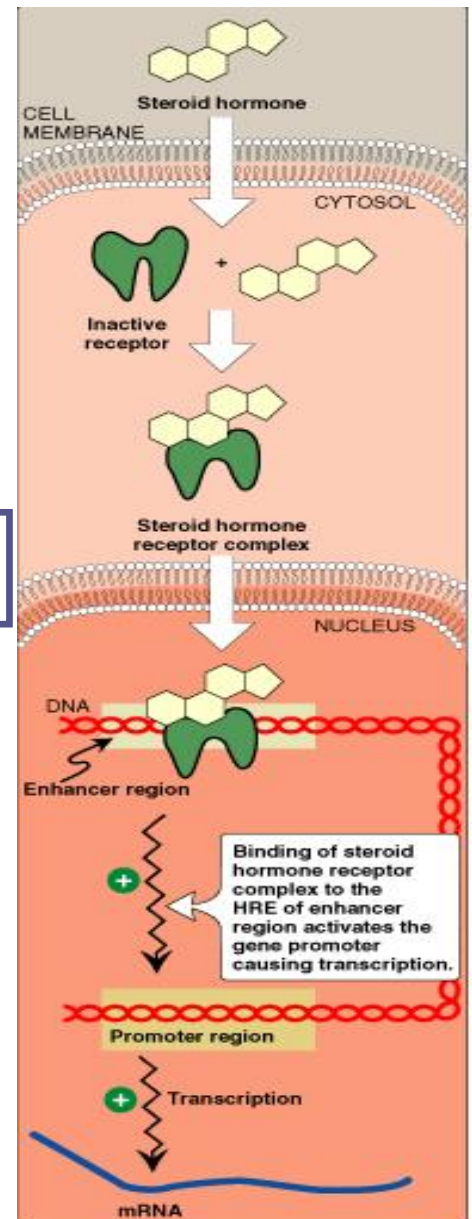
✓ Calcitriol ($1,25[OH]_2-D_3$)

✓ Retinoic acid

- Receptor is either in the cytosol or nucleus (**intracellular**).
- Hormone receptor complex is inside the nucleus.

Mechanism of Action of Steroid-Thyroid Hormones

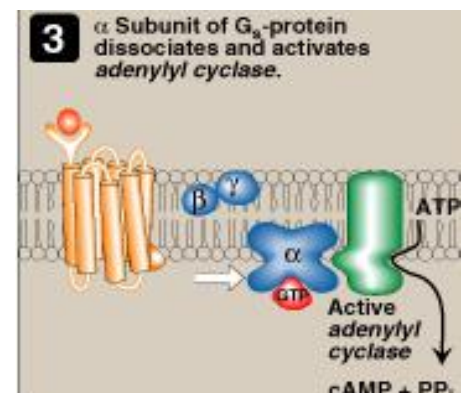
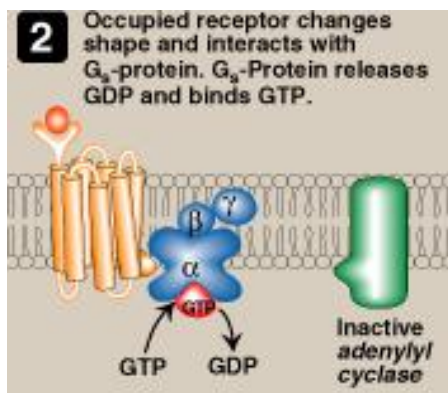
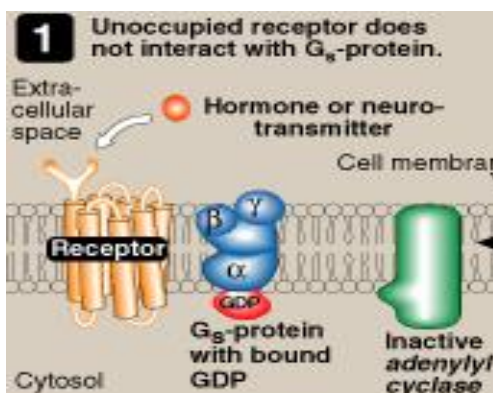
- A hormone passes the membrane bi-layer easily and binds to its receptor to form the hormone-receptor-complex (active form) it then pass into the nucleus to bind to the "hormone-receptor elements" which are elements on the DNA at the **promoter region** (the site of polymerase binding to activate the gene transcription) of a certain gene, these hormones could lead to enhancement or silencing of the gene transcription. Then it gets out of the nucleus to be translated in the cytoplasm.
- The systems shut down when the hormone **detaches** from its receptor.



Group II. Hormones that bind to cell surface receptors

A. The second messenger is cAMP

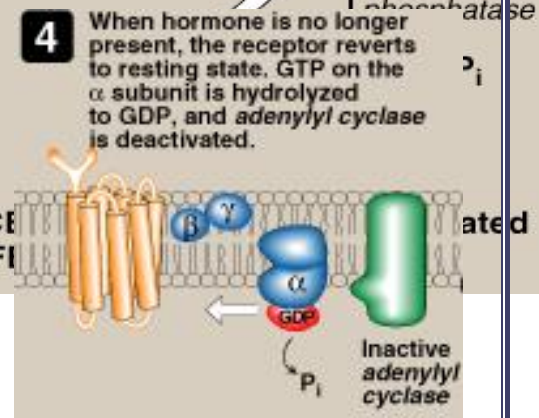
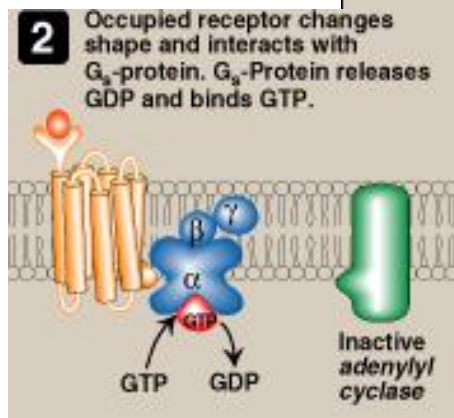
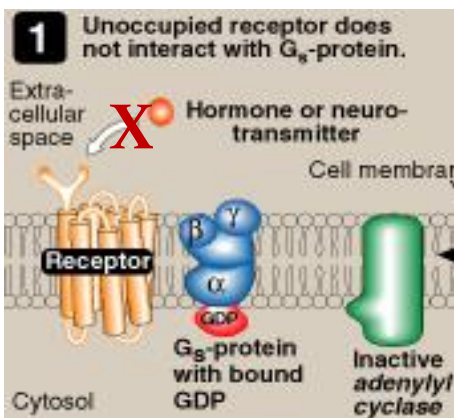
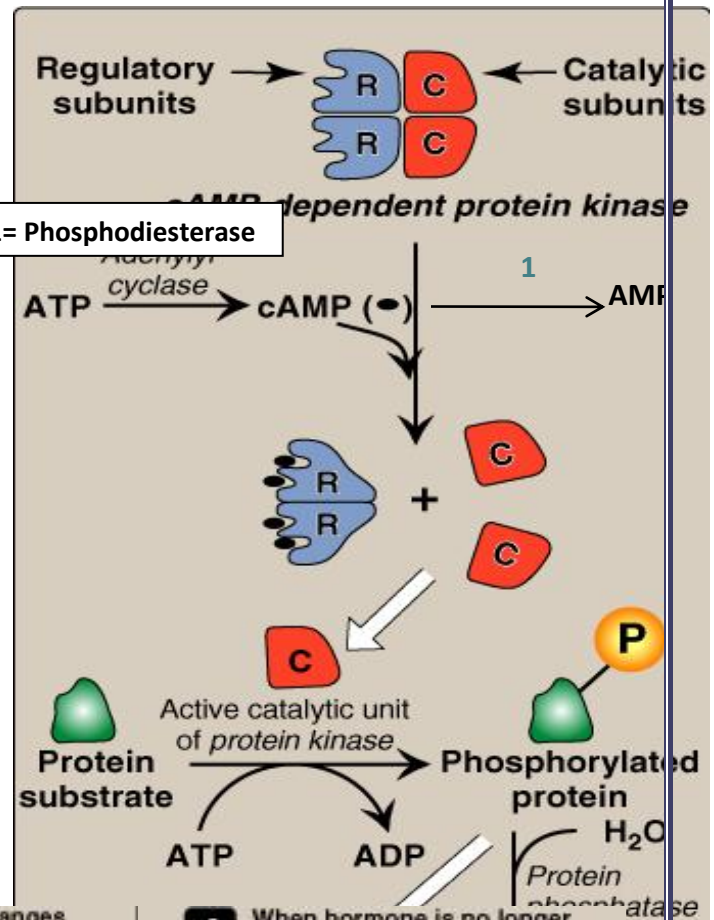
- *Glucagon*
- *Catecholamines (β -Adrenergic)*
- *ADH (Renal V2-receptor)*



Actions of cAMP

- Once hormone is attached to the receptor, GDP is activated and converted to GTP which activates the enzyme Adenyl Cyclase that convert ATP into cAMP that act as a second messenger.
- Protein Kinase (Inactive) is formed of Regulatory and Catalytic subunits.
- Protein kinase is activated when regulatory subunits **dissociate** from the catalytic ones.
- (Activated protein kinase) function is to convert any substrate from the dephosphorylated state to phosphorylated state by adding a phosphate group.
- To inactivate this process:
 - 1- Degradation of the cAMP that activates the removal of the regulatory subunit to AMP by adding an enzyme (Phosphodiesterase).
 - 2- Inactivate the phosphorylation by adding an enzyme (Phosphatase) that will remove the phosphate group (This process works on the target).
- Note that in **cAMP** it's called **Protein Kinase A** and

1= Phosphodiesterase



in **cGMP** it's called **Protein Kinase G**.

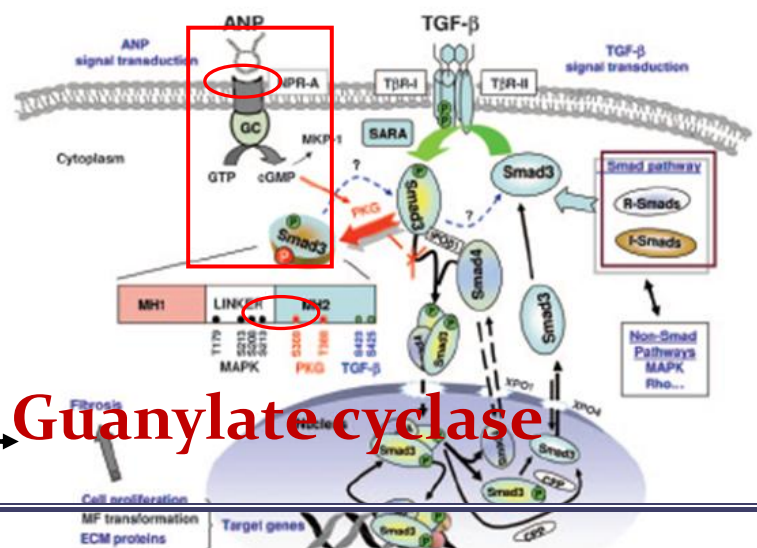
Inhibiting the formation of GTP by adding the enzyme (GTPase) that will convert GTP to GDP.

Group II. Hormones that bind to cell surface receptors

B. The second messenger is cGMP

The activated enzyme is **guanylate cyclase**
For Example: ANP and NO

GC: Guanylate cyclase



Atrial Natriuretic Peptide (ANP)

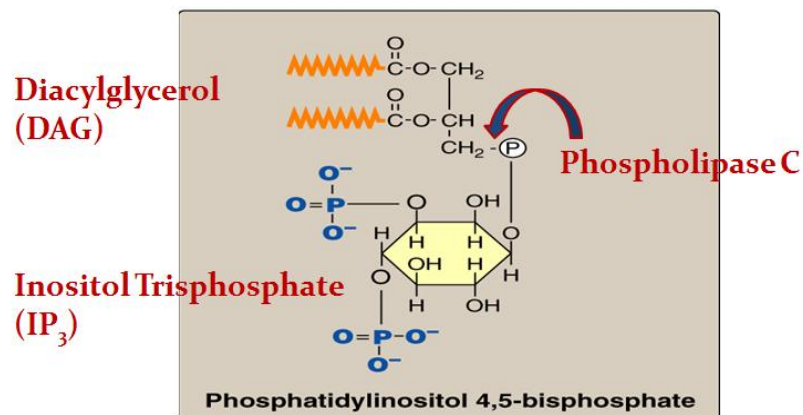
- In this case, NO or ANP binds to the surface receptor and activates **guanylate cyclase** which causes the activation of the second messenger which is **cGMP**.

Group II. Hormones that bind to cell surface receptors

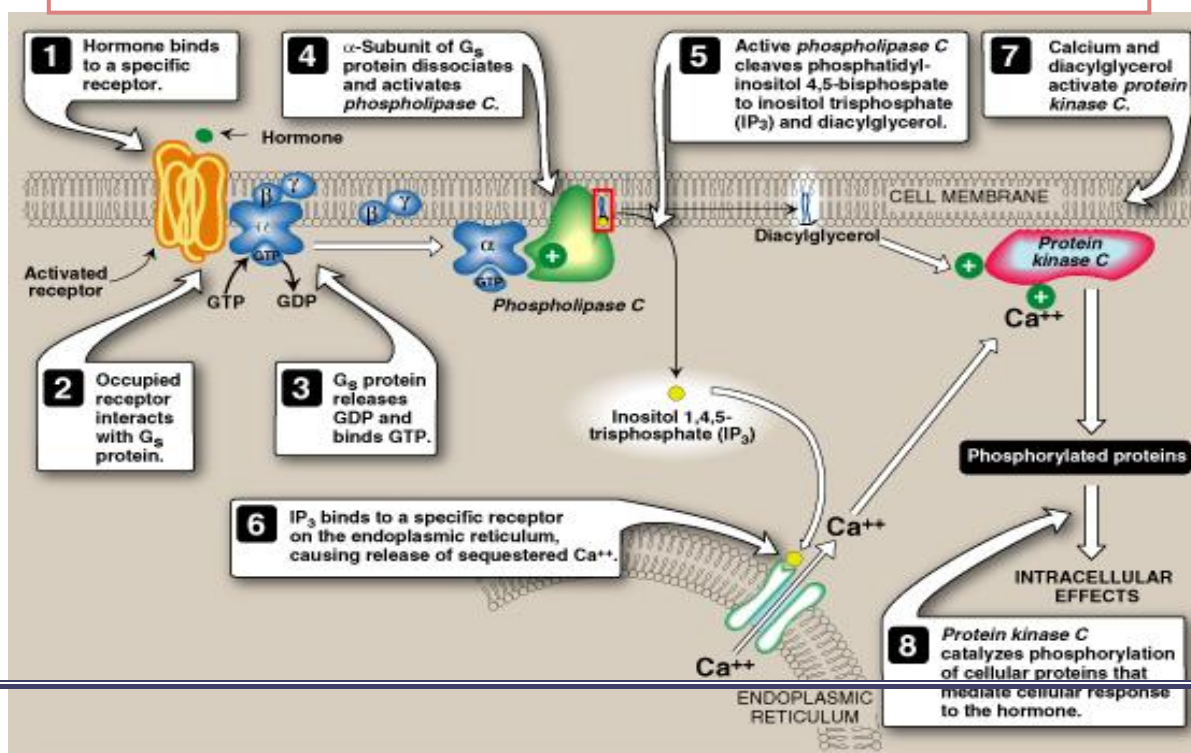
C. The second messenger is calcium or phosphatidylinositol (or both)

- Catecholamines (α_1 -Adrenergic)
- ADH (vasopressin): Extra-renal V1-receptor

Calcium/Phosphatidylinositol System



- 3 mediators: **Diacylglycerol**, **IP₃** that will release **Ca²⁺**.
- Note that in here it's called **Protein Kinase C**.

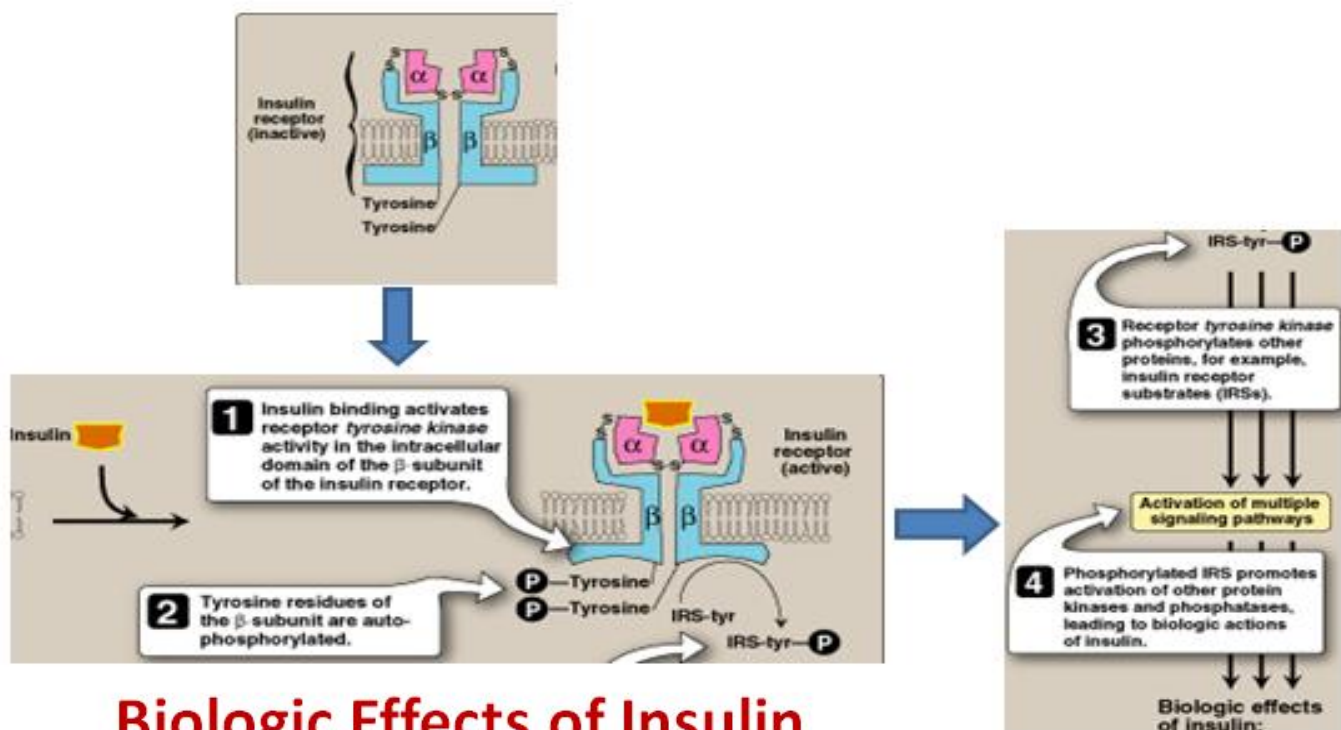


II. Hormones that bind to cell surface receptors

D. The second messenger is a tyrosine kinase cascade

- Insulin
- Growth hormone

Mechanism of Insulin action



Biologic Effects of Insulin



Biomedical Importance

- Excessive, deficient, or inappropriate production /release of hormones are major causes of diseases

- Many drugs act through influencing the pathways of hormones

Summary

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- A target cell is any cell in which the hormone (ligand) binds to its receptor.
- Classification of Hormones by Mechanism of Action:
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 - ADH (Renal V2-receptor)
 - Calcitonin & PTH
 - Glucagon
- B. The second messenger is cGMP:
 - Atrial natriuretic peptide (ANP)
 - Nitric oxide
- C. The second messenger is Calcium or phosphatidylinositol(IP_3) (or both):
 - Acetylcholine (muscarinic)
 - Catecholamines (α_1 - Adrenergic)
 - Angiotensin II
 - ADH (vasopressin): Extra-renal V1-receptor
- D. The second messenger is a tyrosine kinase cascade:
 - GH & Prolactin
 - Insulin
 - Erythropoietin