GENERAL MECHANISMS OF HORMONE ACTIONS

Biochemistry Teamwork

Khalid Al-Khamis	Al-Anood Asiri
Abdulaziz Al-Shamlan	Lama Mokhlis
Abdullah Al-Mazyad	Noha Khalil
Turki Al-Otaibi	Reem Al-Mansour
Meshal Al-Otaibi	Nuha Al-Furayh
Saud Al-awad	Jumana Al-Shammari
Khaled Almohaimede	Deema Jomar
Osamah Al-Jarallah	Fatimah Abdulkarim
	Lamia Alghamdi

Done by: Meshal Al-Otaibi , Abdulaziz Al-Shamlan & Al-Anood Asiri

GENERAL MECHANISMS OF HORMONE ACTIONS

RED COLOR = IMPORTANT

GREEAN COLOR = ADDITIONAL EXPLENATION

Background

- Multicellular organisms depend in their survival on their adaptation to a constantly changing environment
- The secretion of specific hormones occurs to help balance the changed environment back to normal. These hormones work by binding to receptors (located either on:
  - The membrane of cells, which binds to hydrophilic hormones
  - Or intracellularly in the cell's plasma, which binds to: hydrophobic 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
- More than one hormone can affect a given cell type
- Hormones can exert many different effects in one cell or in different cells

After meal: INSULIN is the upper hand hormone (↓ glucose level)

Fasting: GLUCAGON is the upper hand hormone (↑ glucose level)

- A target is any cell in which the hormone (ligand) binds to its receptor

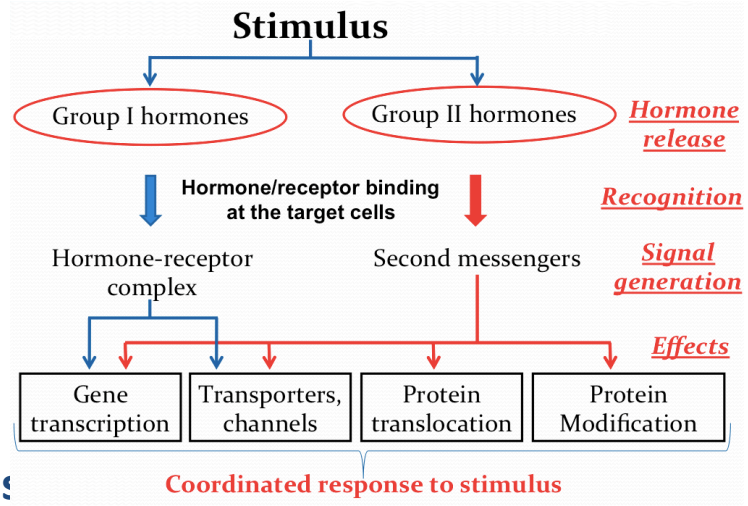
Factors determining the response of a target cell to a hormone:

- The rate of synthesis & secretion of the hormones (availability of the hormone)
- The conversion of inactive forms of the hormone into the fully active forms
  e.g: As in insulin; first it is synthesized as a preprohormone, then to a prohormone and finally to its active form.
- The rate of hormone clearance from plasma (half-life & excretion)
  - Short lived hormones = mostly hydrophilic hormones (minutes)
  - Long lived hormones = mostly hydrophobic hormones (hours/days)
- The number, relative activity, and state of occupancy of the specific receptors, this includes the UP and DOWN regulation of the receptors
- Post-receptor factors. (Happens intracellularly)

The hormone-receptor complex is present in both groups of hormones.

The difference is that the hormone-receptor comeplex in group I is the mediator of the action occurring in the cell (acts just like the second messengers of group II)

The hormone-receptor complex in group II does not mediate the action directly, it has to have a second messenger to mediate the action.



General Features of Hormone Cla

	Group I	Group II
Types	Steroids Thyroid Hormones: (T3 & T4) Calcitriol, retinoids	Polypeptides Glycoproteins Catecholamines
Solubility	Lipophilic (can diffuse into the cell)	Hydrophilic
Transport proteins	Yes	No
Plasma half-life	Long (hours – days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor-hormone complex	Second messengers: cAMP, cGMP, Ca^{2+}, metabolites of complex phosphoinositols, tyrosine kinase cascades

Classification of Hormones by Mechanism of Action:

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

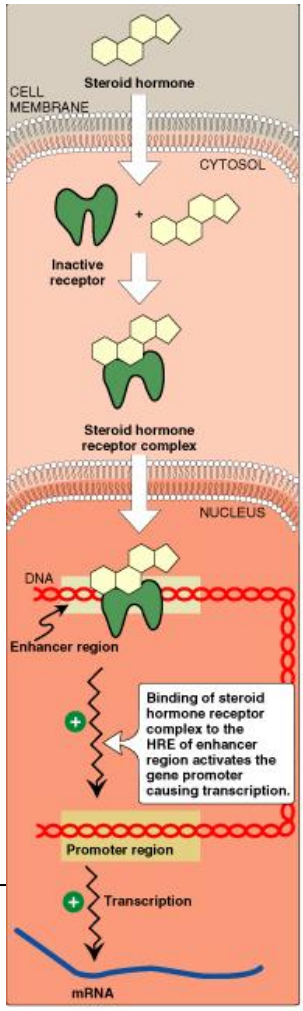
- Steroid hormones
- Thyroid Hormones (T_3 & T_4)
- Calcitriol (active form of vitamin D, $1,25[OH]_2$-D_3)
- Retinoic acid

II. Hormones that bind to cell surface receptors: classified by its second messenger to:

1. cAMP	2. cGMP	3. calcium or phosphatidylinositol (or both)	4. tyrosine kinase cascade
	• Atrial natriuretic peptide (ANP) • Nitric oxide (NO)	• Acetylcholine (muscarinic) • Catecholamines that are bound to α_1-Adrenergic receptors • Angiotensin II • ADH (vasopressin): that is bound to Extra-renal V1-receptor	• GH & Prolactin • Insulin • Erythropoietin

- Catecholamines that are bound to $\alpha 2$ and β Adrenergic receptors
- Ant. Pituitary: ACTH, FSH, LH & TSH • ADH (Renal V2-receptor) • Calcitonin & PTH • Glucagon

Group I. Hormones that bind to intracellular receptors:



Mechanism of Action of Steroid-Thyroid Hormones

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

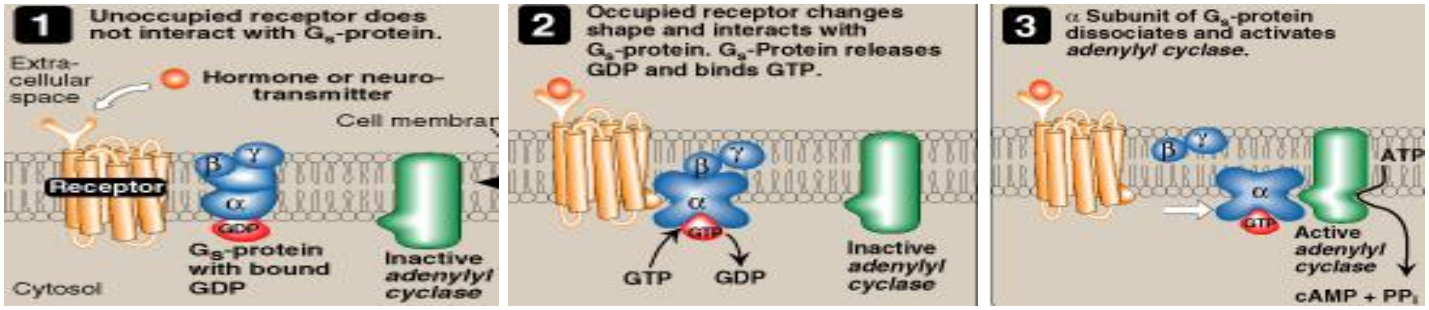
- Receptor is either in cytosol or nucleus.
- Receptor is either Protein or Glycoprotein.
- The hormone pass the cell membrane easily and bind to its receptor to form the hormone receptor complex (Active form). Then, it passes into the nucleus to bind to the hormone receptor elements, which are elements on the DNA at the promoter region (the site of activate the GENE TRANSCRIPTION.
- If the hormone binds to enhancer sequence ➔ stimulation of Gene expression.
- If the hormone binds to silencer sequence ➔repression of Gene expression.

Group II. Hormones that bind to cell surface receptors:

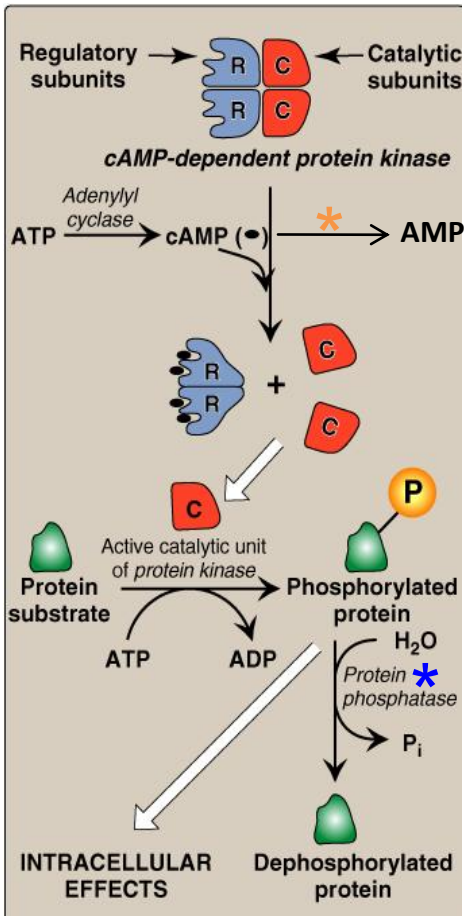
A. The second messenger is cAMP

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

Cascade for formation of cAMP by cell-surface hormones:



Actions of cAMP:

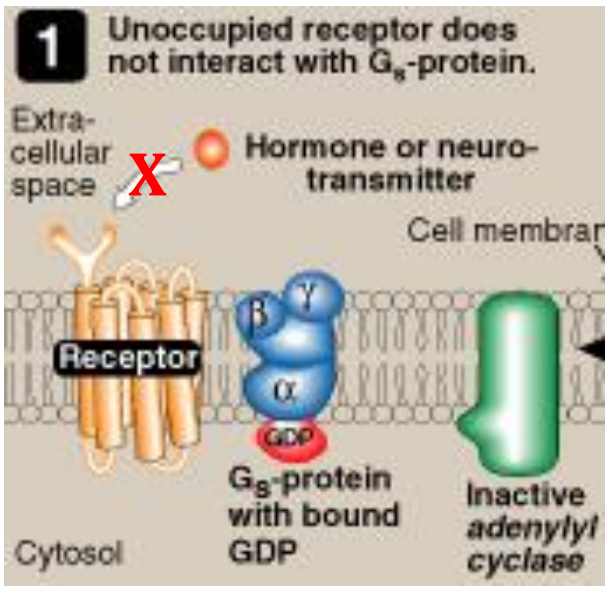


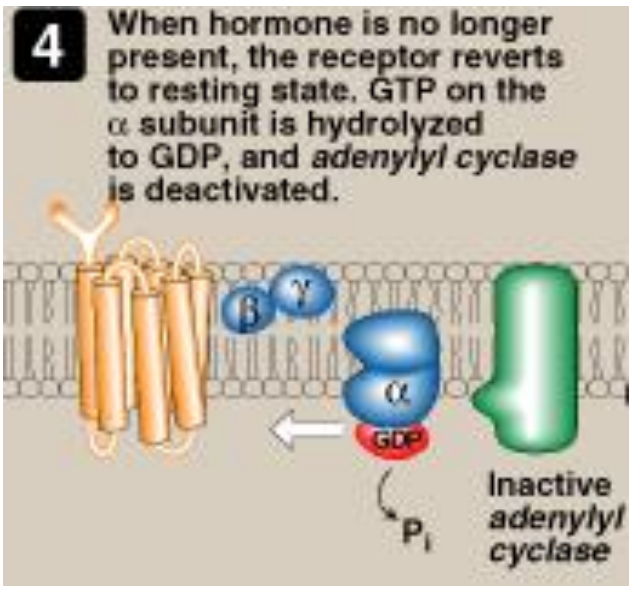
• hormone attaches to its specific receptor on the cell surface, this activates the G-protein subunit to release GDP and attach GTP, and α subunit of the G-protein dissociates and activates adenylyl cyclase.
• Activated adenyly cyclase converts ATP to cAMP, which acts as the second messenger.
• Inactive cAMP-dependent protein kinase A (PKA) is formed of a complex two regulatory and two catalytic subunits. The binding of cAMP to the regulatory subunits of PKA changes its conformation and detaches the catalytic (now active) subunits. the active catalytic subunits phosphorylate target proteins substrates to either activate or inhibit them depending on the protein.

<u>How to inhibit the actions of cAMP:</u>
• giving* Phosphodiesterase to convert cAMP to AMP to block the effect of PKA activation.
• giving* Phosphatase to dephosphorylate whatever the catalytic units phosphorylated
• giving GTPase to convert GTP to GDP to block the activation of adenylyl cyclase.

Abortion of Hormonal Stimulus :

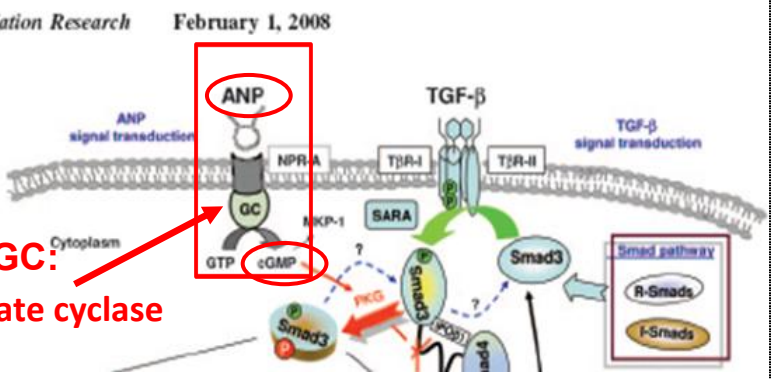
- Release of hormone from its receptor (unbound receptor)
- Dephosphorylation of protein substrate by phosphatase
- Degradation of cAMP into AMP by phosphodiesteras
- Inactivation of protein kinase A by a decrease of cAMP
- Hydrolysis of GTP into GDP
- Binding of α-subunit to βγ-subunits
- Inactivation of adenylyl cyclase





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: Gunaylate cyclase

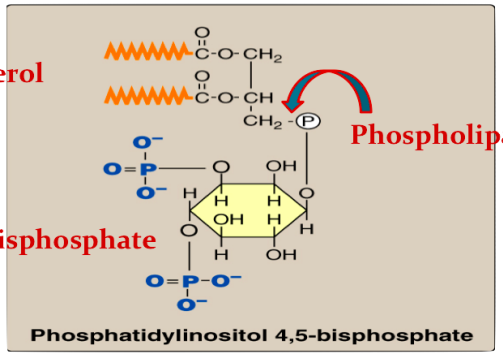
In this case, NO or ANP binds to the surface receptor and activates ***guanylate cyclase*** which converts GTP to cGMP ➔ the second messenger.

Group II. Hormones that bind to cell surface receptors:

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

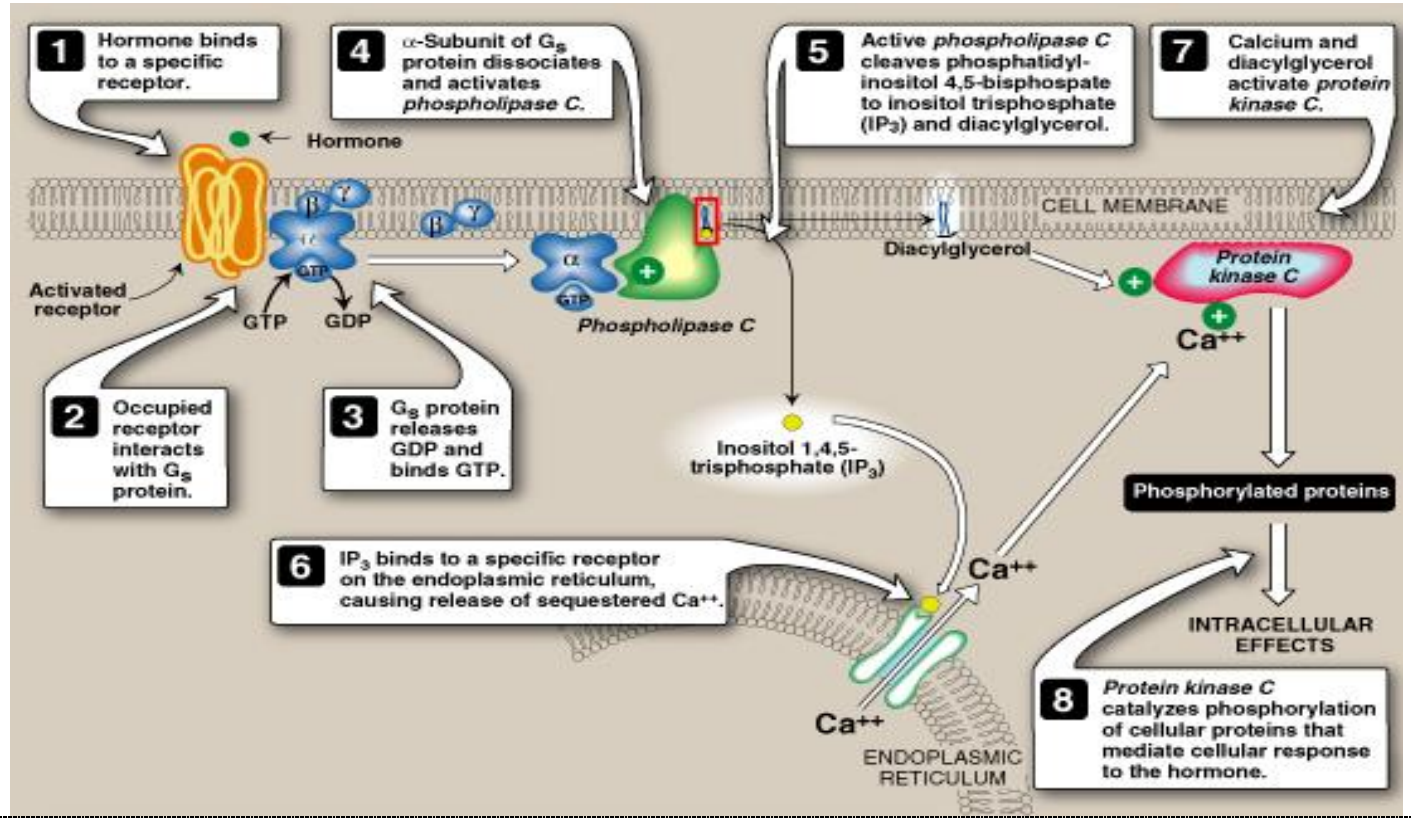
- Catecholamines (α1-Adrenergic)
- ADH (vasopressin): Extra-renal V1-receptor

Calcium/Phosphatidylinositol System:



2 mediators: **Diacylglycerol + IP3** that will realease **Ca^{+2}**
Note that in here it's called **Protein Kinase C.**

Phospholipase C : acts on lipids. Protein kinase C : acts on proteins.

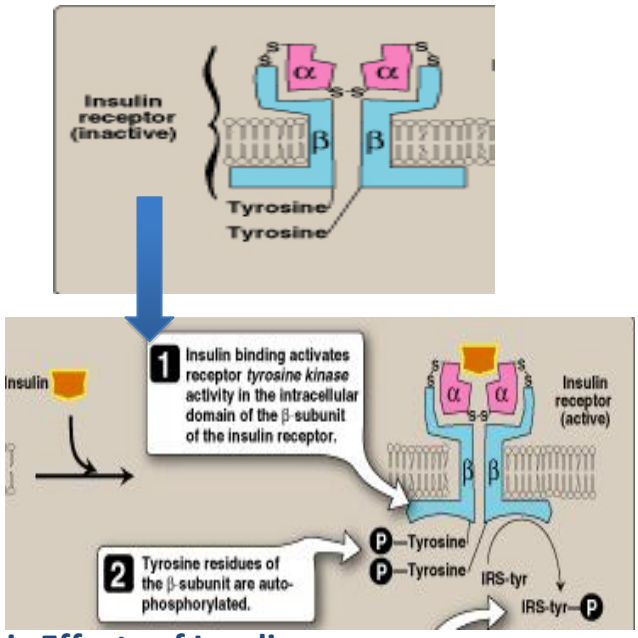


II. Hormones that bind to cell surface receptors

D. The second messenger is a tyrosine kinase cascade

- Growth hormone and prolactin
- Insulin
- Erythropoietin

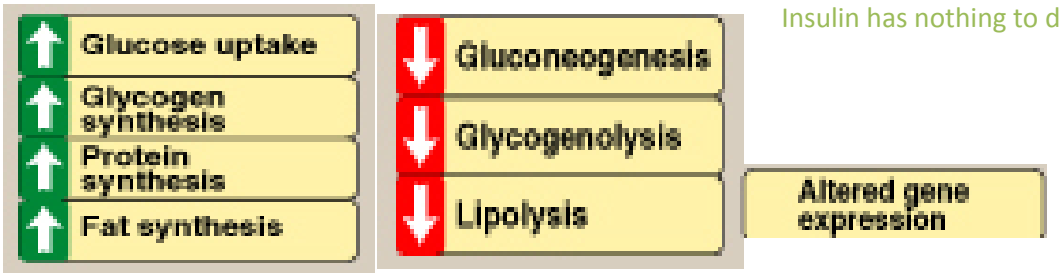
Mechanism of Insulin action



Here: Receptor itself is phosphorylated (autophosphorylation) and gets activated as an enzyme. It phosphorylates IRS-tyrosine (insulin receptor substrate).

Insulin has nothing to do with cAMP.

Biologic Effects of Insulin



Biomedical Importance

Excessive (e.g., hyperthyroidism, Cushing), deficient (e.g., hypothyroidism, Addison), or inappropriate secretion (e.g., syndrome of inappropriate secretion of ADH "SIADH") of hormones are major causes of diseases

Pharmacological treatment of these diseases depends on replacement of deficient hormone (*hypo-*) or use of drugs that interfere with the mechanism of action of the hormones (*hyper- or inappropriate*)

Questions:

1. Hormone that binds to a cell surface receptor and requires the second messenger camp is :

(A) Antidiuretic hormone

(B) Cholecystokinin

(C) Calcitriol

(D) Gastrin

2. All the following statements about steroid hormones are true except

(A) They are hydrophobic

(B) They require carriers to transport them in circulation

(C) Their receptors are intracellular

(D) They require cyclic AMP as second messenger

3. Glycogenoloysis is decreased by

(A) Glucagon (B) Insulin (C) Epinephrine (D) cAMP

4. G-proteins act as

(A) Hormone carriers

(B) Hormone receptors

(C) Second messengers

(D) Signal transducers

1- A 2- D 3- B 4- D