

GENERAL MECHANISMS OF ACTIONS OF HORMONE

* Please check out [this link](#) to know if there are any changes or additions.

Revised by

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Color index: **Important** | **Doctors notes** | Further explanation.

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:

- **Multicellular** organisms depend in their survival on their **adaptation** to a constantly changing environment.
- **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.
- **A target** is: any cell in which the **hormone** (ligand) **binds to its receptor**.

BIOMEDICAL IMPORTANCE OF HORMONES:

- ❖ **Excessive** (e.g., hyperthyroidism, Cushing “cortisol”), **deficient** (e.g., hypothyroidism, Addison “cortisol & aldosterone”), or **inappropriate secretion** (e.g., syndrome of inappropriate secretion of ADH “SIADH”) of hormones are major causes of diseases.

بس اللي يوصله ان الهرمونات لها أهمية طبية وانها تسبب امراض لو صار فيها خلل "زيادة نقصان" .. والمتلازمات المذكورة بناخذ عنهم محاضرات كاملة.

- ❖ **Pharmacological treatment of these diseases depends on:**

- **Replacement of deficient hormone** (hypo-)
- **Drugs that interfere with the mechanism of action of the hormones** (hyper- or inappropriate).

وهنا يقول ان علاج هذي الامراض بيكون اما اننا نعطي الشخص الهرمون "لو كان السبب نقص" أو اننا نعطيه دواء يعرقل الآلية اللي يشتغل فيها الهرمون..

FACTORS DETERMINING THE RESPONSE OF A TARGET CELL TO A HORMONE

- 1 The **rate** of **synthesis & secretion** of the hormones
- 2 The **conversion** of **inactive forms** of the hormone into the **fully active form**
- 3 The **rate** of **hormone clearance** from **plasma** (half-life & excretion)
- 4 The **number, relative activity, and state** of **occupancy** of the specific receptors
- 5 **Post-receptor factors**

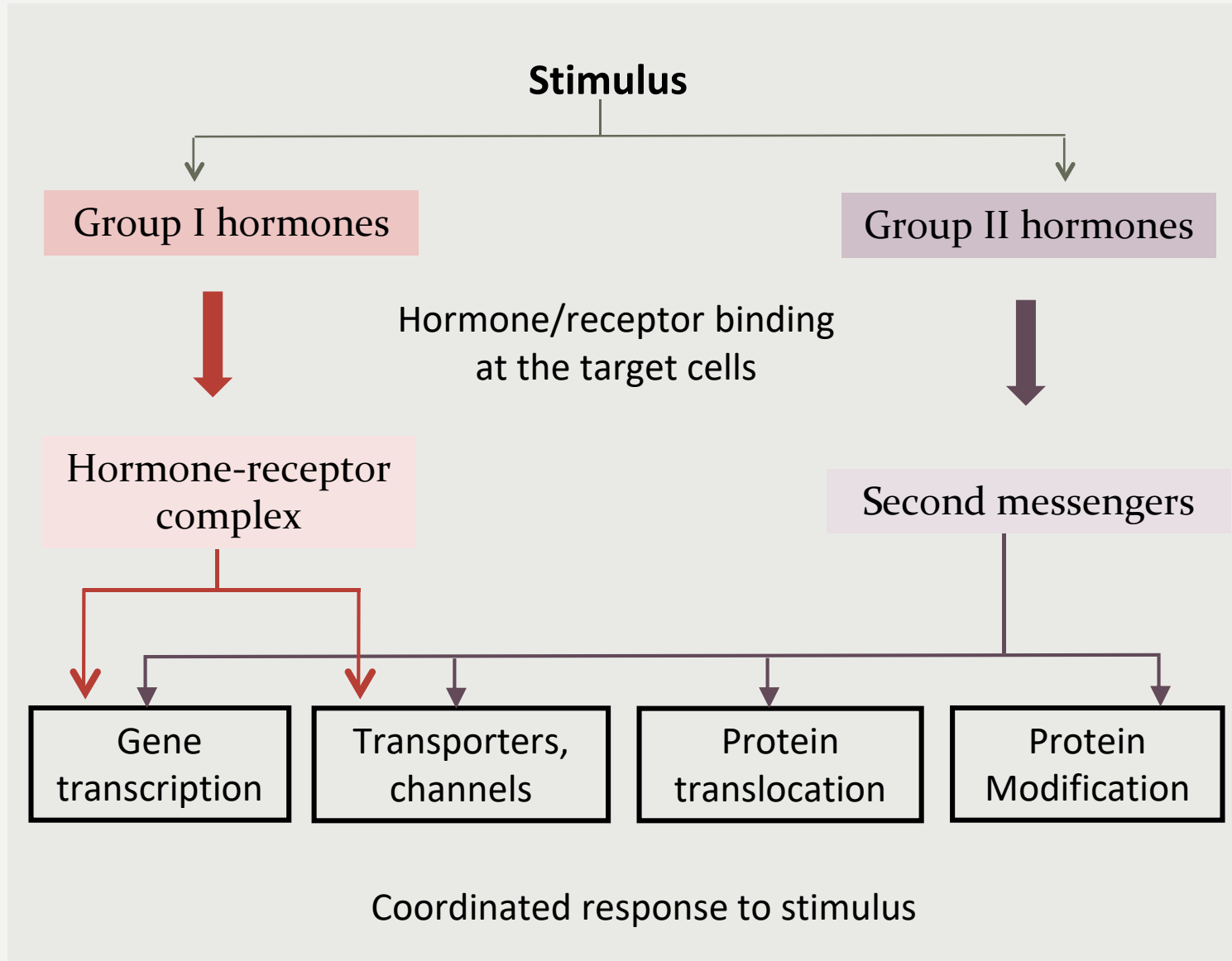
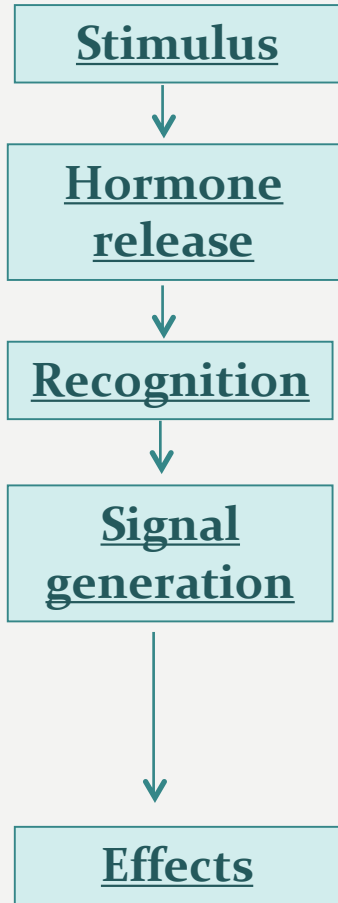
تخلي رحلة الهرمونات..

تصنع ← تفرز ← تتحول لاكتف فورم ← تروح للبلازما ← ترتبط بالريسبتور الموجود على الخلية ← يبدأ تأثيرها "سواء بسكند ماسنجر أو مباشرة.. بينتكلم عن

هالشيء بالتفصيل"

كل هذي الأشياء تمثل عوامل تحدد استجابة الخلية للهرمون

GENERAL FEATURES OF HORMONE CLASSES:



هذه الشريحة بتختصر عليكم حفظ الشريحة القادمة..
قسمت الهرمونات الى مجموعتين بناء على مكان الرستور..

*المجموعة الاولى:

- الرستور بيكون داخل الخلية.
- ليش؟ لأنها لايبوفيلك فتعدي الغشاء بكل سهولة وتروح ترتبط مع الرستور داخل الخلية وتكون كومبلكس وتأثر على الخلية.

*المجموعة الثانية:

- مكان الارتباط بيكون على الميمبرين!
- ليش؟ اكيد لأنها محبة للماء فماتقدر تمر وبتقعد برا.
- طيب هي برا كيف تقدر تأثر على الخلية؟

ترسل سكند ماسنجر "كأنه نائب ينوب عنها ويوصل رسالتها"

(ميب زي المجموعة الأولى اللي ارتبطت بالرستور وكونت كومبلكس وكان نظامها "رجلي على رجلك يا رستور").

GENERAL FEATURES OF HORMONE CLASSES:

	Group I	Group II
Types	<ul style="list-style-type: none"> • Steroids • Thyroid Hs (T3 & T4) • Calcitriol, retinoids 	<ul style="list-style-type: none"> • Polypeptides • Glycoproteins • Catecholamines
Solubility	Lipophilic	Hydrophilic.
Transport proteins	Yes	No
Plasma half-life	Long (hours – days) They're usually bound to proteins	Short (minutes) ليه؟ لأنها تنتقل بدون ترانسبورتير فهي عرضة للتكسير
Receptor	Intracellular	Plasma membrane
Mediator \ signal recognition	Receptor-hormone complex	cAMP, cGMP, Ca ²⁺ , metabolites of complex phosphoinositols, tyrosine kinase cascades
Effects	1-Gene transcription. 2-Transporters, channels.	1-Gene transcription 2-Transporters, channels 3-Protein translocation 4-Protein Modification

Classification of Hormones by Mechanism of Action

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

❖ Examples:

➤ **Steroid Hormones:**

- **Glucocorticoids**
- **Mineralocorticoids**
- **Sex hormones:**

- ✓ **Male sex hormones:** Androgens
- ✓ **Female sex hormones:** Estrogens & Progestins

➤ **Thyroid Hormones (T3 & T4)**

➤ **Active form of vitamin D, 1,25[OH]₂-D₃**

➤ **Retinoic acid:** A metabolite of vitamin A (retinol) that is required for growth and development.

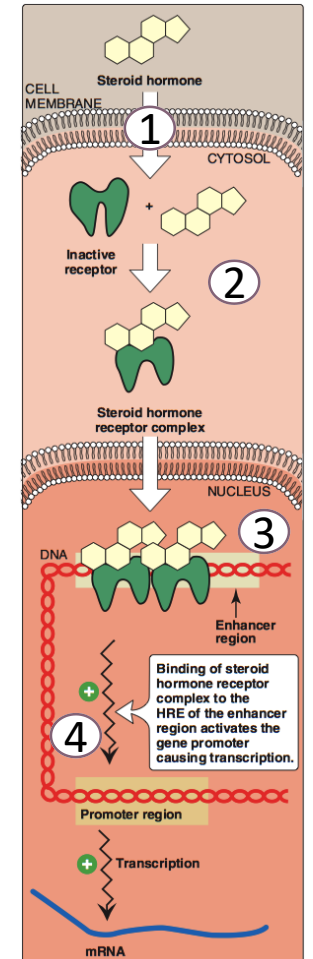
The action of this group usually is on the gene level (sometimes on the protein level).

Group II. Hormones that bind to cell surface receptors

❖ Mechanism:

- 1- Steroid hormones **diffuse** across the plasma membrane of its target cell.
- 2- **Binds** to a specific “Cytosolic like steroid hormones” or “Nuclear like thyroid hormone” receptor and forms “Receptor ligand complex”.
- 3- That complex **accumulates, dimerizes,** and **binds** to hormone response element (**HRE**) “a specific regulatory DNA sequence” in association with either coactivator or corepressor.
- 4- This cause **promotor activation\inhibition** and **increased\decreased** transcription of the targeted gene **depending on the hormone**.

All types of group 1 enter the cell **passively** except **T3 & T4**, they enter the cell actively (need ATP).



Classification of Hormones by Mechanism of Action

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

Group II. Hormones that bind to cell surface receptors

A. The second messenger is cAMP

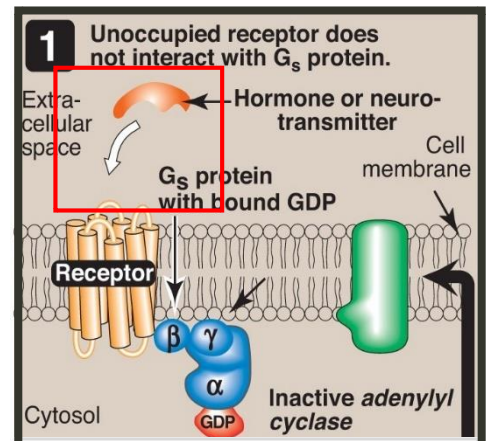
❖ Examples:

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

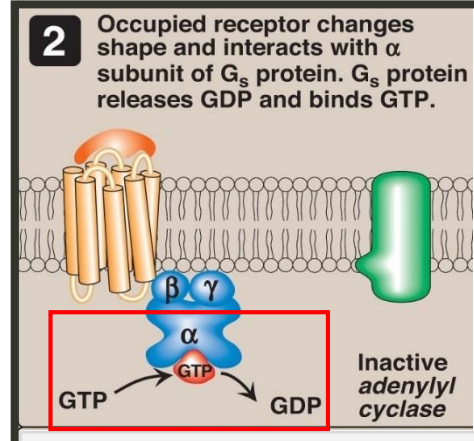
ركزوا انها الفا تو

[Second Messenger system : cAMP](#)

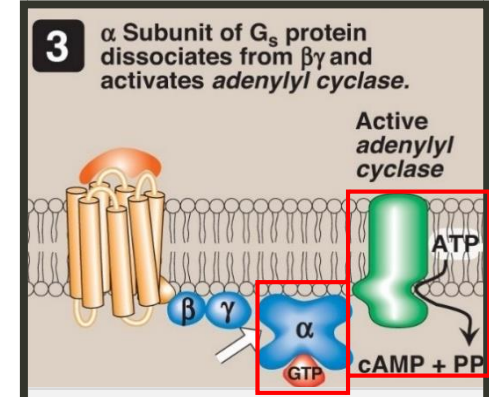
❖ Mechanism:



1- **Binding** of ligand "Hormone" causes a conformational change in the receptor.



2- Replacement of the GDP of the G-protein " α subunit" with GTP.



3- GTP-bound form of the alpha subunit dissociates from the beta and gamma subunits and move adenylyl cyclase "AC", which is thereby activated.

cAMP

cGMP

calcium or phosphatidylinositol (or both)

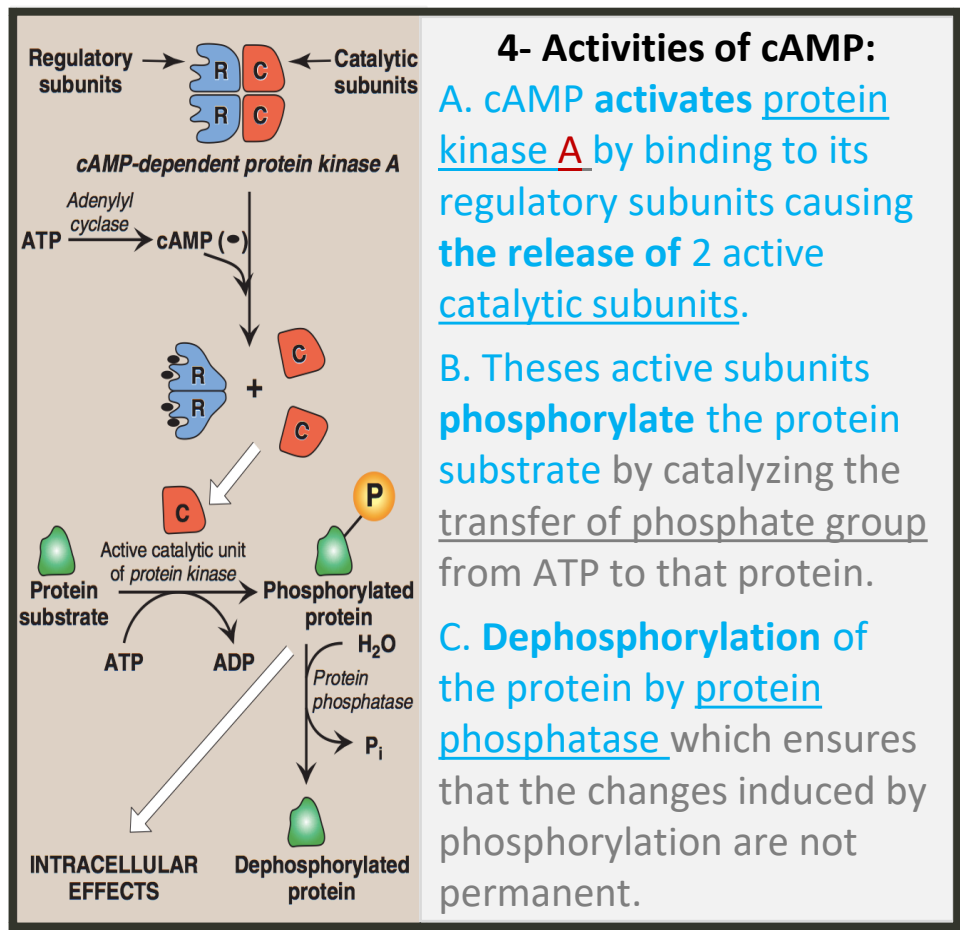
tyrosine kinase cascade

Classification of Hormones by Mechanism of Action

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

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❖ Mechanism:



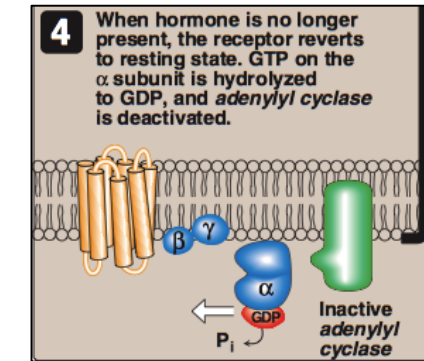
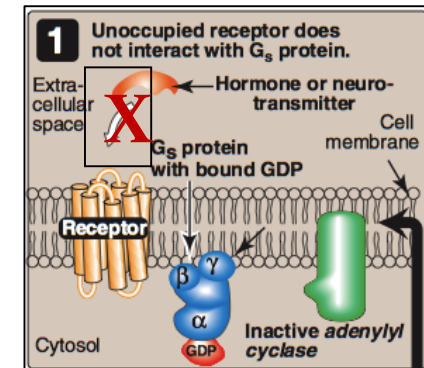
4- Activities of cAMP:

- A. cAMP activates protein kinase A by binding to its regulatory subunits causing the release of 2 active catalytic subunits.
- B. These active subunits phosphorylate the protein substrate by catalyzing the transfer of phosphate group from ATP to that protein.
- C. Dephosphorylation of the protein by protein phosphatase which ensures that the changes induced by phosphorylation are not permanent.

❖ Abortion of Hormonal Stimulus

1. **Release** of hormone from its receptor (unbound receptor).
2. **Dephosphorylation** of protein substrate by **phosphatase**.
3. **Degradation** of cAMP into AMP by **phosphodiesterase**.
4. Inactivation of protein kinase A by a **decrease** of cAMP.
5. **Hydrolysis** of GTP into GDP.
6. **Binding** of α-subunit to βγ-subunits.
7. **Inactivation** of adenylyl cyclase.

(alpha subunit has an intrinsic GTPase activities so it can hydrolyze GTP back to GDP)



- cAMP
- cGMP
- calcium or phosphatidylinositol (or both)
- tyrosine kinase cascade

Classification of Hormones by Mechanism of Action

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

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B. The second messenger is cGMP

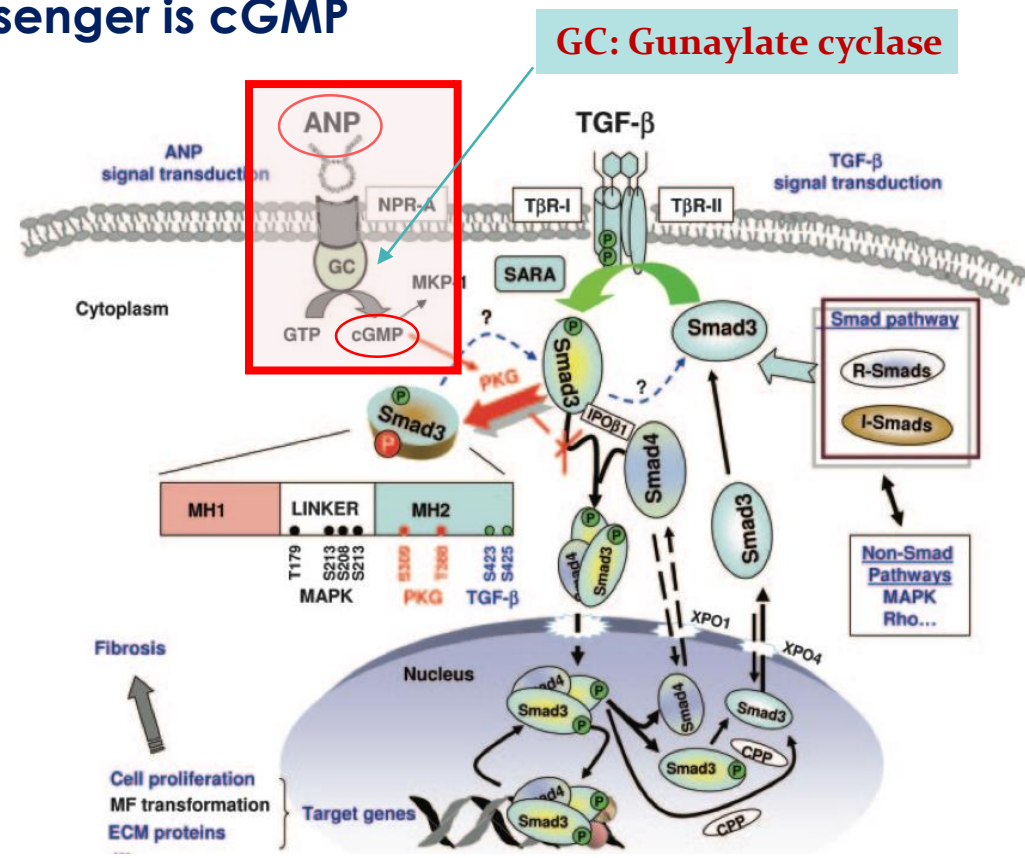
❖ Examples:

- ✓ Atrial natriuretic peptide (ANP).
- ✓ Nitric oxide (NO).

❖ Mechanism:

1. ANP binds to natriuretic peptide receptor (NPR).
2. Direct activation of **Gunaylate cyclase**.
3. Activated GC converts GTP to cGMP.
4. Then cGMP exerts its function.

هنا المکانزم بسيطة وما فيها أي تعقيدات الهرمون من يرتبط بالرسبتور ←
 بيحفز الجي سي اللي بيعطينا السكند ماسنجر (خطوتين: ارتباط - تحفيز
 الجي سي)..
 عكس المجموعة اللي تكلمنا عنها بالشرائح السابقة اللي تحتاج لجي بروتين
 علشان تحفز الاي سي اللي بيعطي السكند ماسنجر (3 خطوات: ارتباط -
 جي بروتين - تحفيز الأي سي).



أهم شيء بالصورة هو اللي مظل بالأحمر

- cAMP
- cGMP
- calcium or phosphatidylinositol (or both)
- tyrosine kinase cascade

Classification of Hormones by Mechanism of Action

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

Group II. Hormones that bind to cell surface receptors

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

❖ Examples:

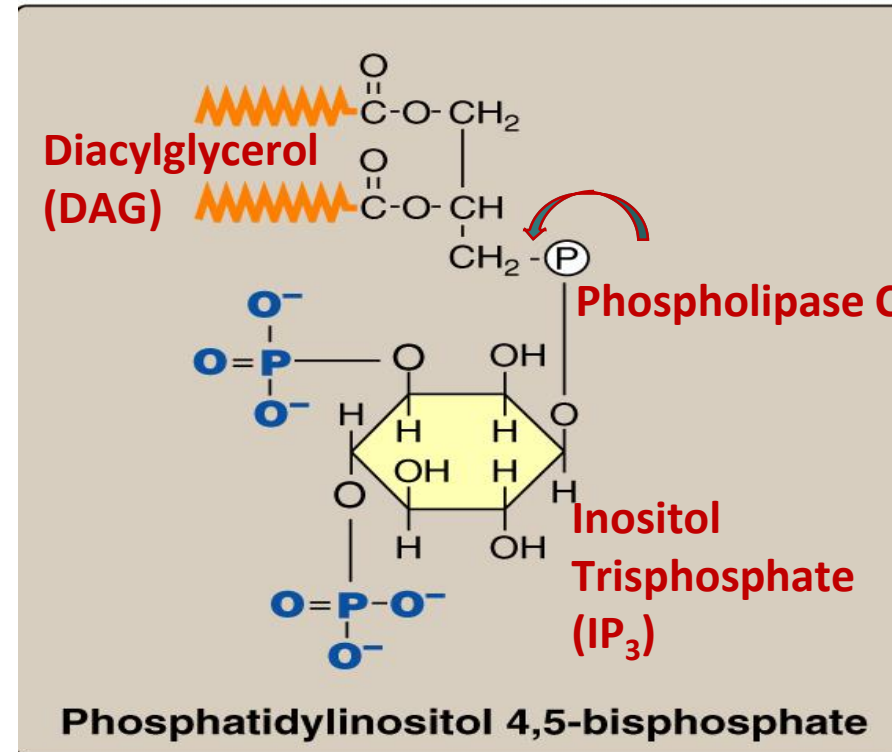
- ✓ **Acetylcholine** (muscarinic)
- ✓ **Catecholamines** (α 1- Adrenergic)
- ✓ **Angiotensin II**
- ✓ **ADH** (vasopressin): **Extra**-renal **V1**-receptor.

There are 3 subtypes of vasopressin receptor (V1,2,3).
 $V_1 \rightarrow$ phosphatidylinositol/calcium + vasoconstriction effect.
 $V_2 \rightarrow$ Adenylyl cyclase/cAMP + antidiuretic effect.

❖ Calcium/Phosphatidylinositol (PI) System:

- PI is synthesized from:
Free inositol + Diacylglycerol -as shown in the figure-.
- **Phospholipase C** hydrolytically cleaves **phosphatidylinositol 4,5-bisphosphate** "phosphorylated form of PI" to:

Diacylglycerol (DAG) + Inositol Trisphosphate (IP_3).



cAMP

cGMP

calcium or
phosphatidyl-
inositol
(or both)

tyrosine
kinase
cascade

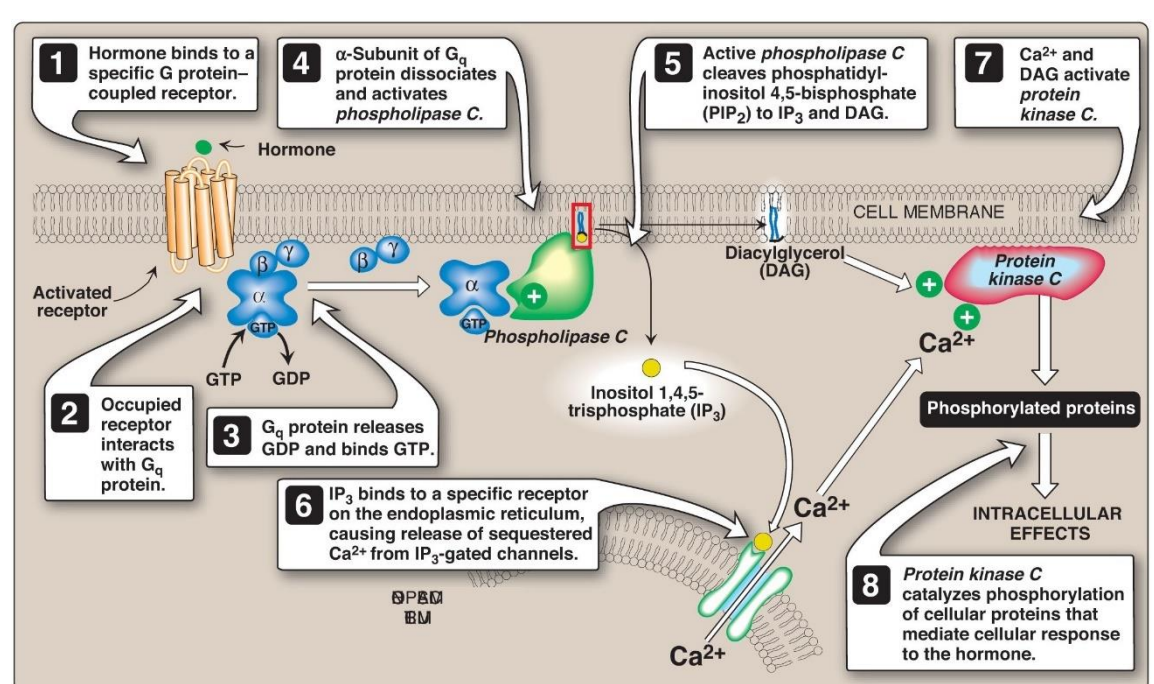
Classification of Hormones by Mechanism of Action

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

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❖ **Mechanism:**

1. Hormone **binds to G-protein coupled receptor**.
- 2&3. Receptor **Interacts with G-protein** Which **releases GDP** and binds with **GTP**.
4. Alpha subunit **dissociates from $\beta\gamma$ -subunits**, and **activates Phospholipase C**.
5. Phospholipase **cleaves phosphatidylinositol 4,5-bisphosphate to DAG and IP₃** "as we mentioned in the previous slide".
6. IP₃ **binds to a specific receptor on RER** causing release of **Ca**.
7. **Calcium and DAG synergistically** activate protein kinase **C** (C because it requires calcium).
8. Protein kinase C catalyzes protein phosphorylation.



cAMP

cGMP

calcium or phosphatidylinositol (or both)

tyrosine kinase cascade

لاحظوا ان الاكتيشفين هنا بيكون للبروتين كائينز سي!

There are 3 types of G protein: I, S, & Q. I & S types activate cAMP (like the one we mentioned in slide 9), while Q activate cGMP (notice it in the white bubble no. 2 above)

[PIP2 secondary message system](#)

Classification of Hormones by Mechanism of Action

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

Group II. Hormones that bind to cell surface receptors

D. The second messenger is a tyrosine kinase cascade

- ❖ **Examples:**
 - ✓ GH & Prolactin
 - ✓ **Insulin**
 - ✓ Erythropoietin

❖ Biologic Effects of Insulin:



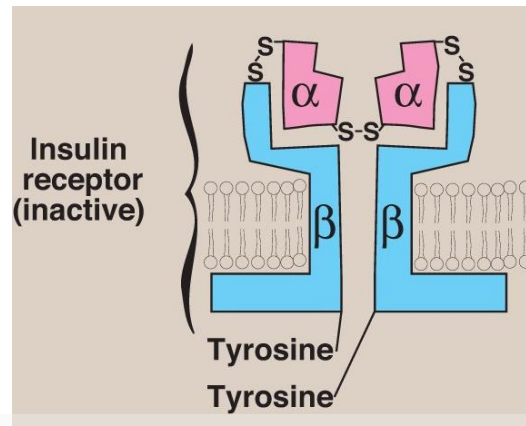
- Glucose up take → Indirectly
- Glycogen synthesis
- Protein synthesis
- Fat synthesis



- Gluconeogenesis.
- Glycogenolysis.
- Lipolysis.

+ Altered gene expression

❖ Insulin receptor:



Insulin receptor is a **dimer** that consists of 2 identical units. Each unit has:

- ***An alpha-chains:** on the **outside** and create a **binding site** for insulin.
- ***A beta-chains:** Spans the **plasma membrane** and its cytosolic domain is a **tyrosine kinase**.

Subunits are bound together by disulfide bond.

cAMP

cGMP

calcium or phosphatidylinositol (or both)

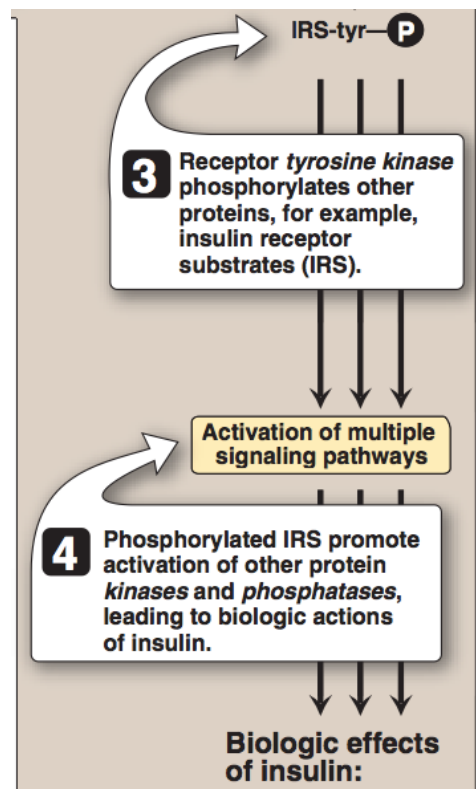
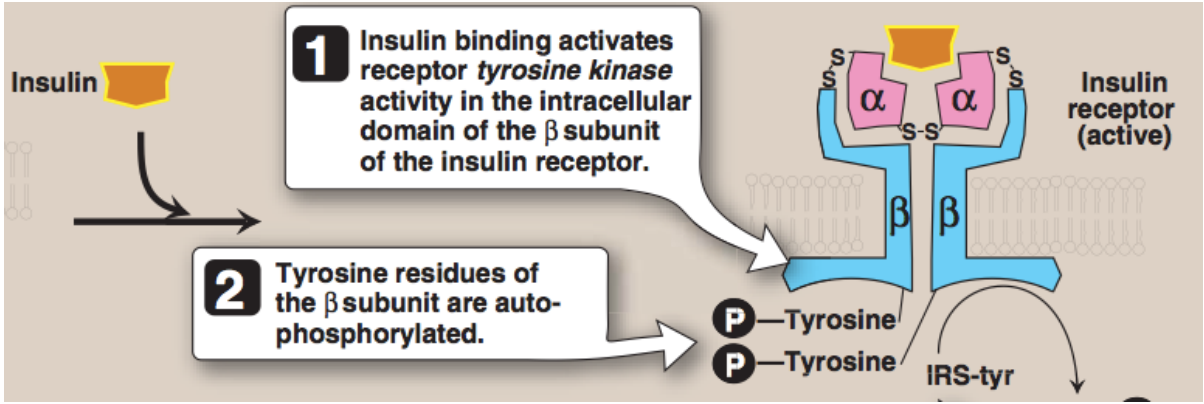
tyrosine kinase cascade

Classification of Hormones by Mechanism of Action

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

Group II. Hormones that bind to cell surface receptors

❖ **Mechanism of Insulin action:**



cAMP

cGMP

calcium or phosphatidylinositol (or both)

tyrosine kinase cascade

Binding of insulin to the alpha-subunit → **conformational changes** that are transmitted to β -subunit → **Rapid autophosphorylation** of tyrosine residues of the β -subunits → Then **phosphorylation of insulin receptor substrates (IRS)** "a family of proteins" by **tyrosine kinase** → **Activation of other protein kinases and phosphatases by IRS** → **Biological actions of insulin.**

[Insulin Signal Transduction Pathway](#) "very helpful"

Check your understanding!

1. When ADH binds to its extra renal V1 receptor , its second messenger will be?

- A. CA/phosphatidylinositol (Ca/PIP)
- B. cAMP
- C. cGMP
- D. Tyrosine kinase

2. Which one of the following hormones uses tyrosine kinase cascade as a second messenger?

- A. Prolactin
- B. ADH
- C. Acetylcholine

3. Which one of the following is a biological effect of insulin?

- A. Increase gluconeogenesis
- B. Decrease lipolysis
- C. Increase glycogenolysis
- D. Decrease glucose uptake

4. In CA/phosphatidylinositol system , the function of diacylglycerol is?

- A. To activate protein kinase A
- B. To activate protein kinase C
- C. To activate protein kinase G
- D. To release calcium from endoplasmic reticulum

5. Which one of the following is hydrophilic?

- A. Glucocorticoids
- B. Progesterin
- C. Epinephrine
- D. Retinoic acid

6. In cGMP pathway , protein kinase G activated by:

- A. Adenylyl cyclase
- B. Phospholipase
- C. Protein kinase A
- D. Guanylate cyclase

7. Which one of the following has the longest plasma half life :

- A. Thyroxin
- B. Epinephrine
- C. ADH
- D. PTH

8. The second messenger for atrial natriuretic peptide is :

- A. cAMP
- B. cGMP
- C. Tyrosine kinase
- D. Ca

Done by:

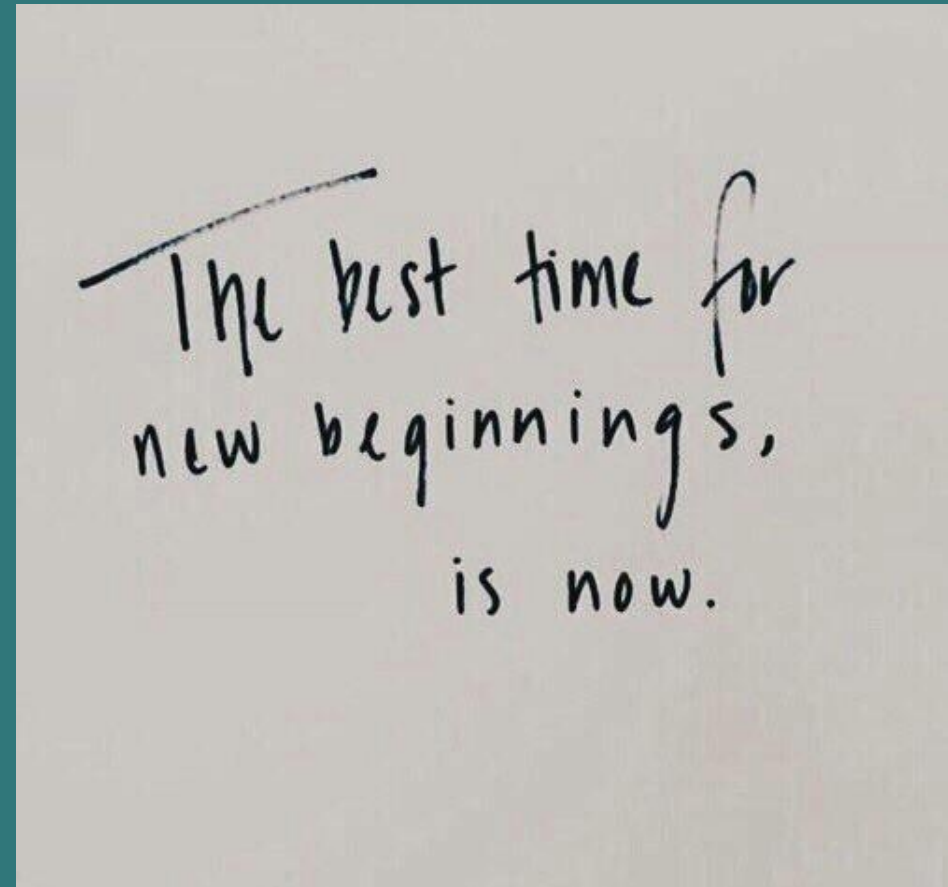
- شهد العنزي.
- عبدالله الغزي
- ابراهيم الشايع
- عاصم الوهيبي
- عبدالله الفريح

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Resources:

- 435's slides and notes.
- Lippincott's illustrated reviews: Biochemistry – sixth edition.
- [Vasopressin receptors V1a and V2 are not osmosensors](#) – National center for biotechnology information.



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