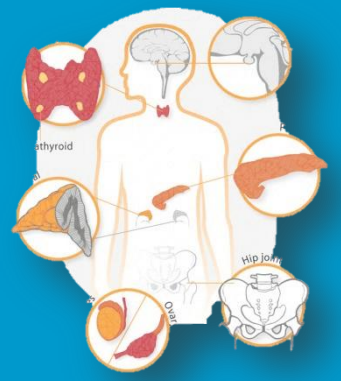
[lecture 1]

General Mechanisms of Hormone Actions



ENDOCRINE SYSTEM

Biochemistry Team

The Objectives

By the end of this lecture, students should be able to:

- 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.

Red = Imp

Blue = explain

Green = addition notes

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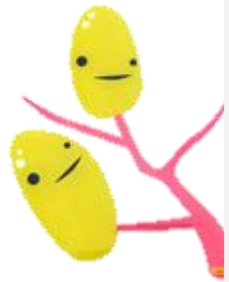
Mind Map

Mind Map

- Background
- Factors determining the response of a target cell to a hormone
- Hormone-receptor interaction
- General features of hormone classes
- Classification of hormones by mechanism of action
- **Biomedical importance**



Background

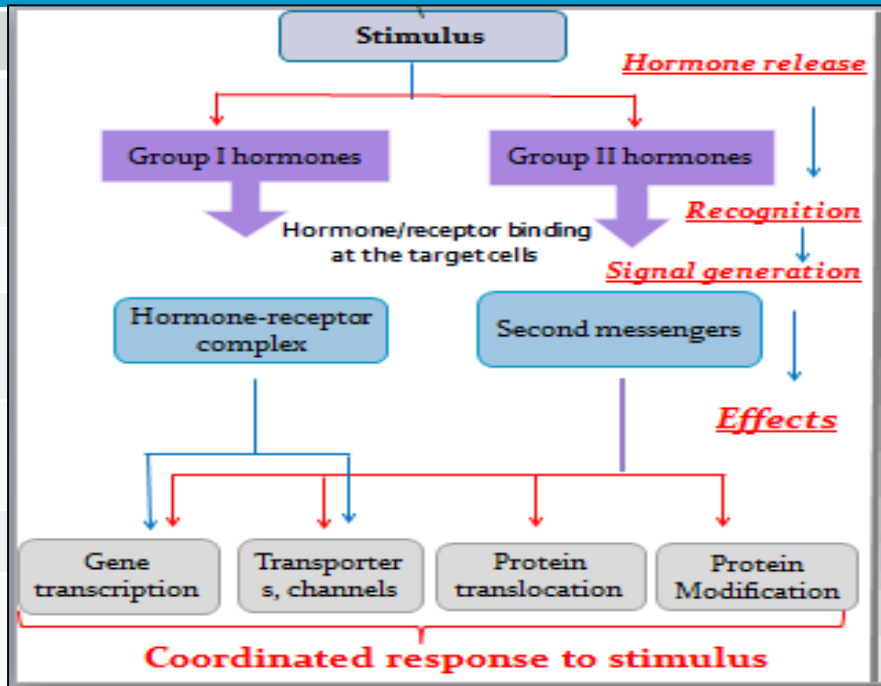
- Multicellular organisms depend in their survival on their adaptation to a constantly changing environment
- Intercellular communication is necessary for this adaptation to take place
- Human body synthesizes many hormones that can act specifically on different cells of the body
- More than one hormone 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

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
- The rate of hormone clearance from plasma (half-life & excretion)
- The number, relative activity, and state of occupancy of the specific receptors
- Post-receptor factors

General Features of Hormone Classes

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

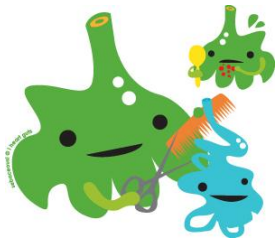


Classification of Hormones by Mechanism of Action

Med432 Biochemistry Team

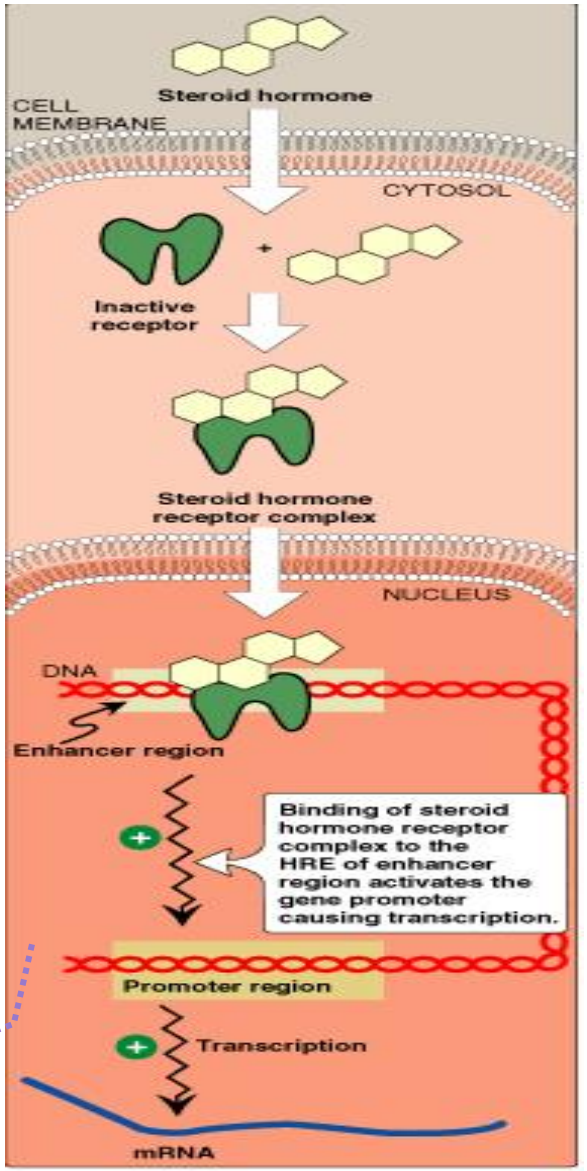
I. Hormones that bind to intracellular receptors (Steroid-Thyroid superfamily)	Steroid hormones Thyroid Hormones (T_3 & T_4) Calcitriol (active form of vitamin D, $1,25[OH]_2$-D_3) Retinoic acid			
	A. The second messenger is cAMP	**B. The second messenger is cGMP**	**C. The second messenger is calcium or phosphatidylinositol ((or both**	**D. The second messenger is a tyrosine kinase cascade**
II. Hormones that bind to cell surface receptors	•Catecholamines (α_2- Adrenergic) • Catecholamines (β- Adrenergic) •ADH (Renal V2-receptor) • Ant. Pituitary: ACTH, FSH, LH & TSH • Glucagon •Calcitonin & PTH	Atrial natriuretic peptide (ANP) Nitric oxide	• Acetylcholine (muscarinic) • Catecholamines (α_1- Adrenergic) • Angiotensin II • ADH (vasopressin): Extra-renal V1-receptor	Growth Hormone (GH) & Prolactin Insulin Erythropoietin

Group I. Hormones that bind to intracellular receptors



- **Group I**
  - 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 element, which are element on the DNA → the DNA will undergo conformational change → activation of a promoter region (the site of activate the GENE TRANSCRIPTION). A Promoter region can be enhancer or silencer.
- If the hormone binds to enhancer sequence → stimulation of Gene expression.
- If the hormone binds to silencer sequence → repression of Gene expression.

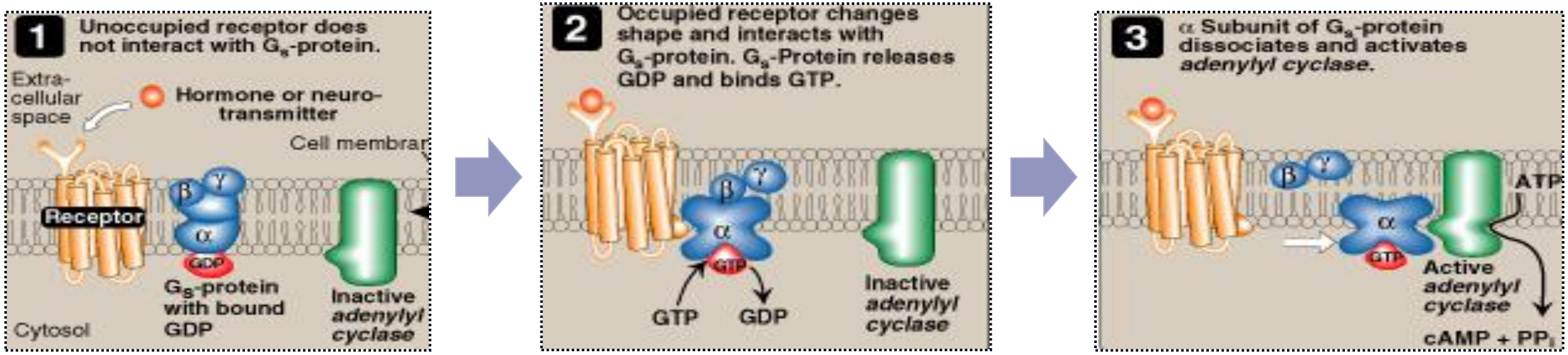


Group II. Hormones that bind to cell surface receptors

A. The second messenger is cAMP :

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

Cascade for formation of cAMP by cell-surface hormones :



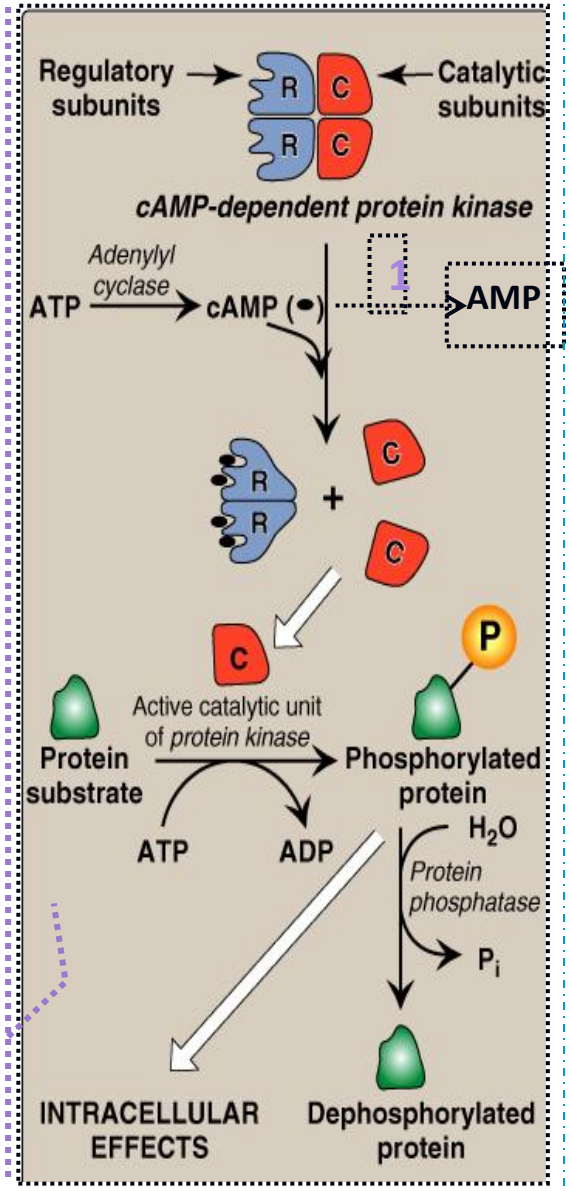
Group II. Hormones that bind to cell surface receptors

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 protein substrates to either activate or inhibit them depending on the protein.

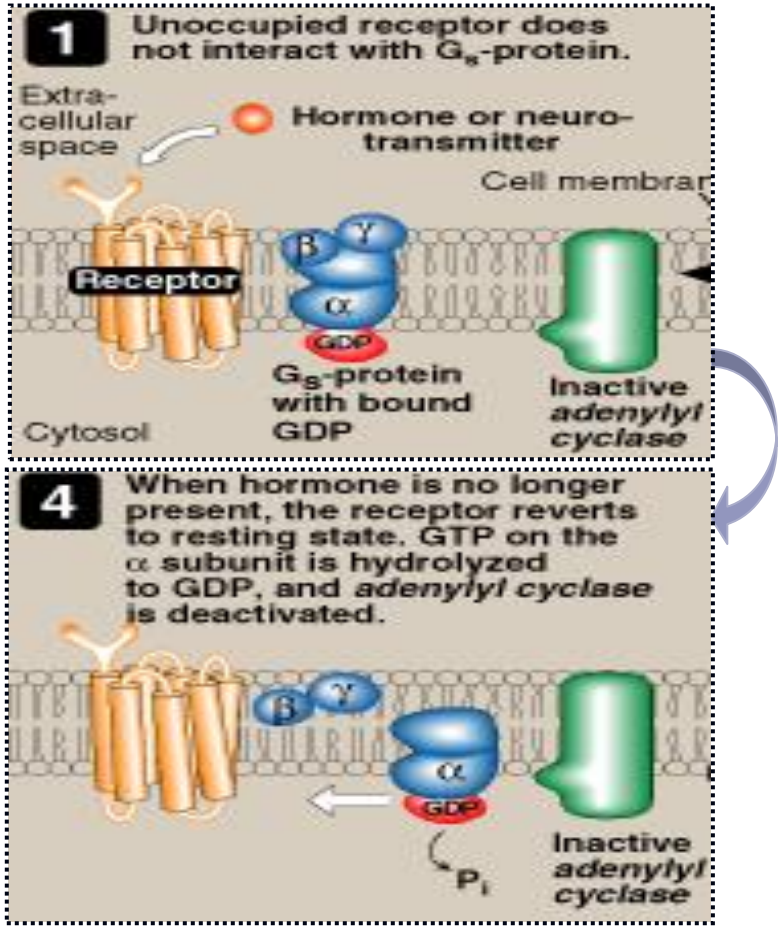
This will be stop if :

- Hormone dissociate from receptor.
- alpha subuint has an intrinsic GTPase activity → convert GTP to ADP → AC will be inactive.
- giving Phosphodiesterase to convert cAMP to AMP to block the effect of PKA activation.
- giving Phosphatase to dephosphorylate whatever the catalytic units phosphorylated



Abortion of Hormonal Stimulus :

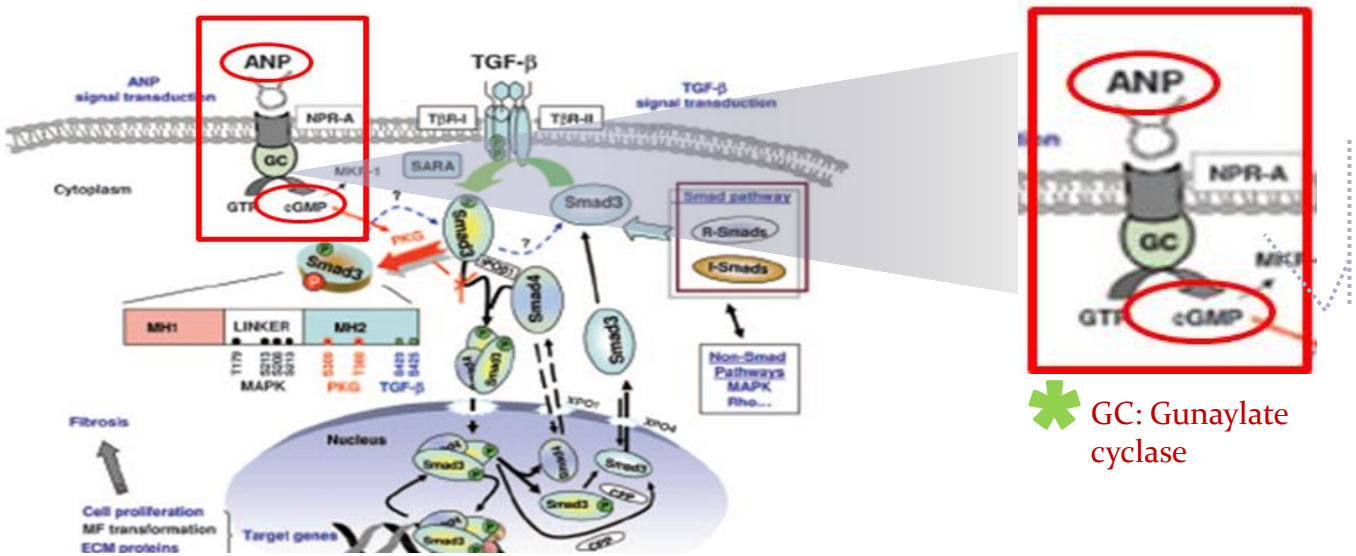
1.Release of hormone from its receptor (unbound receptor)
2.Dephosphorylation of protein substrate by phosphatase
3. Degradation of cAMP into AMP by phosphodiesterase
4.Inactivation of protein kinase A by a decrease of cAMP
5. Hydrolysis of GTP into GDP
6. Binding of α-subunit to βγ-subunits
7.Inactivation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



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

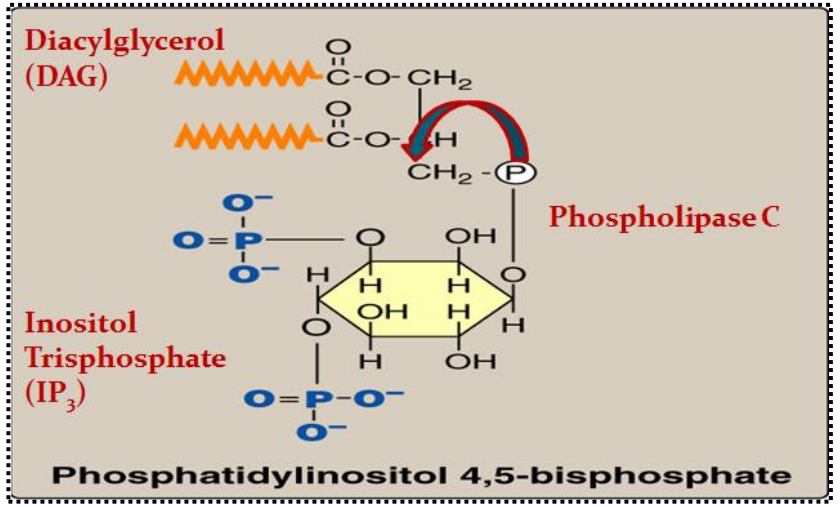


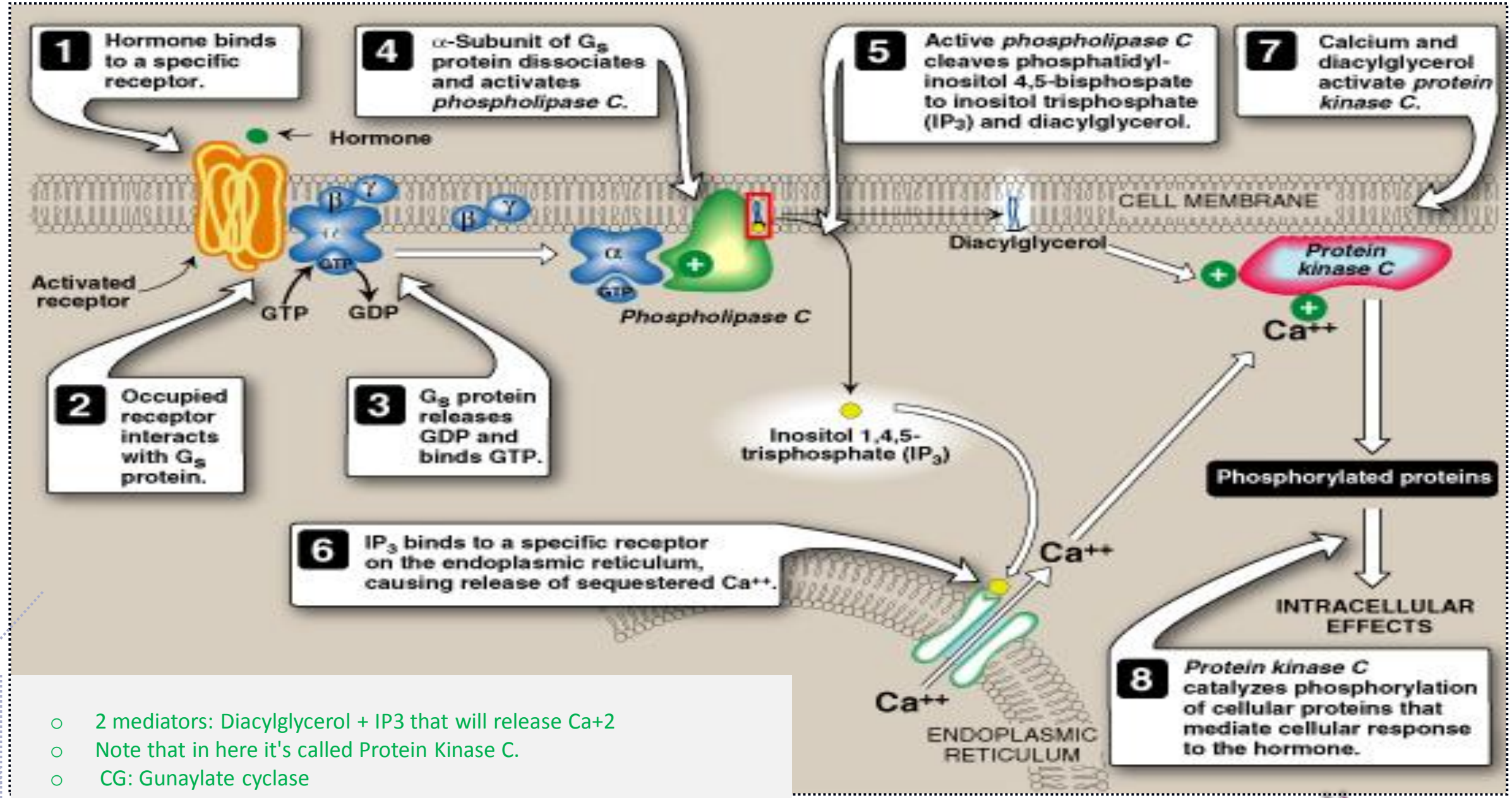
GC Converts GTP to cGMP (2nd messenger)

GC: Gunaylate cyclase

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

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



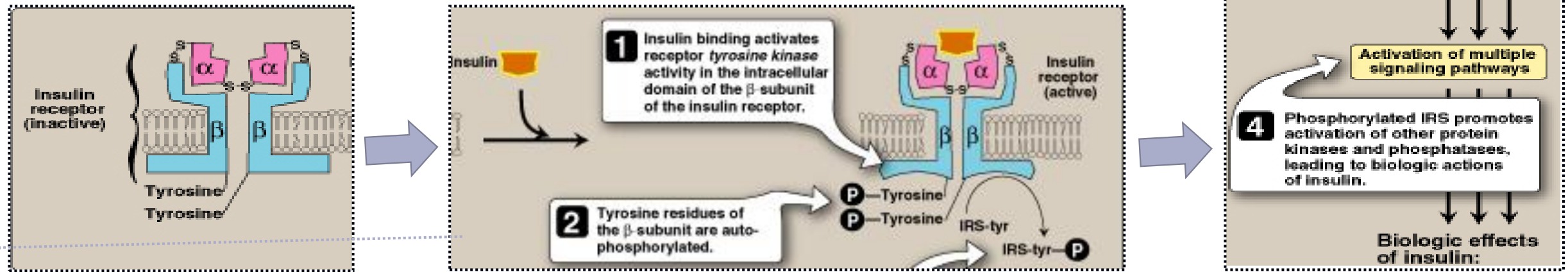


- 2 mediators: Diacylglycerol + IP3 that will release Ca+2
- Note that in here it's called Protein Kinase C.
- CG: Gunaylate cyclase
- Phospholipase C : acts on lipids. Protein kinase C : acts on proteins.

D. The second messenger is a tyrosine kinase cascade

- Growth hormone and prolactin
- Insulin
- Erythropoietin

Mechanism of Insulin action :



- alpha subunit : responsible for recognizing and binding to insulin (contains insulin binding domain), beta : responsible for intracellular effect (contains the tyrosine residue that will be phosphorylated after binding to the insulin) → receptor will be active and undergo conformational changes.
- Receptor itself is phosphorylated (autophosphorylation) and gets activated as an enzyme. It phosphorylates IRS- tyrosine (insulin receptor substrate).

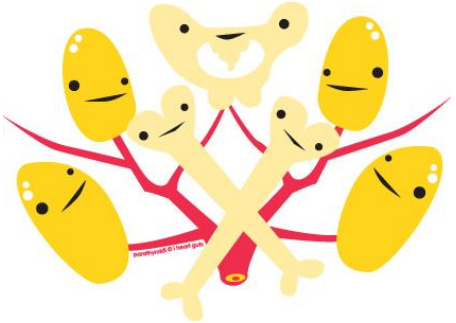
Biologic Effects of Insulin :

Anabolic effect	Decrease glucose levels	
↑ Glycogen synthesis ↑ Glucose uptake ↑ Protein synthesis ↑ Fat synthesis ↑ lipolysis	↓ Gluconeogenesis ↓ Glycogenolysis	Altered gene expression

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*)



Summary

Hormones divide into :

Group I (Steroids , Thyroid Hormones: (T3 & T4) Calcitriol and retinoids , Wich are lipophilic and the receptor is intracellular (either in cytosol or nucleus) , The hormones bind to its receptor to form the hormone receptor complex .

Group II (Polypeptides,Glycoproteins and Catecholamines , Wich are hydrophilic and the receptor is in plasma membrane , the hormones bind to to its receptor by 4 mechanism :

A. The second messenger is cAMP :

- Glucagon , Catecholamines **(β- Adrenergic)** and ADH (Renal V2-receptor) .
- *The activated enzyme is* Adenylyl Cyclase.

B. The second messenger is cGMPB :

- *ANP and NO*
- *The activated enzyme is Guanylate Cyclase*

C. The second messenger is Ca phosphatidylinositol (or both) :

- Catecholamines **(α_1-Adrenergic)** and ADH (vasopressin, Extra-renal V1-receptor)
- *The activated enzyme is* Phospholipase C .

D. The second messenger is a tyrosine kinase cascade :

- Growth hormone , prolactin , Insulin and Erythropoietin.

Test your knowledge ..!

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 Lipophilic
(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

Biochemistry
Team

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