Human Cycle Module
Academic year
2026-2027
Biochemistry

كليات الريان
AL-RAYAN COLLEGES

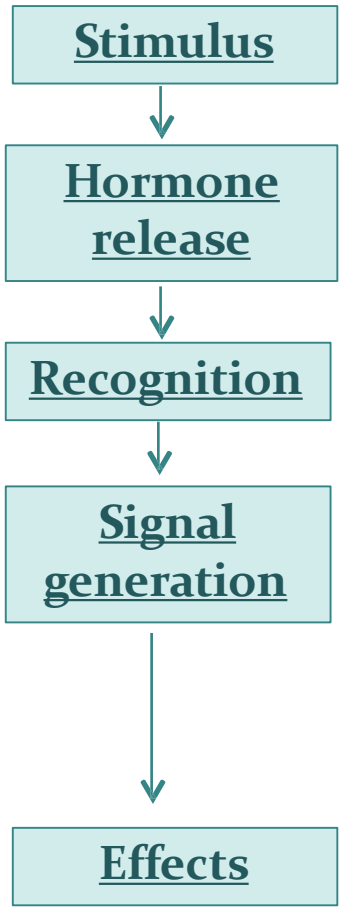
SIGNAL TRANSDUCTION
Mechanism Of Action Of Protein Hormones

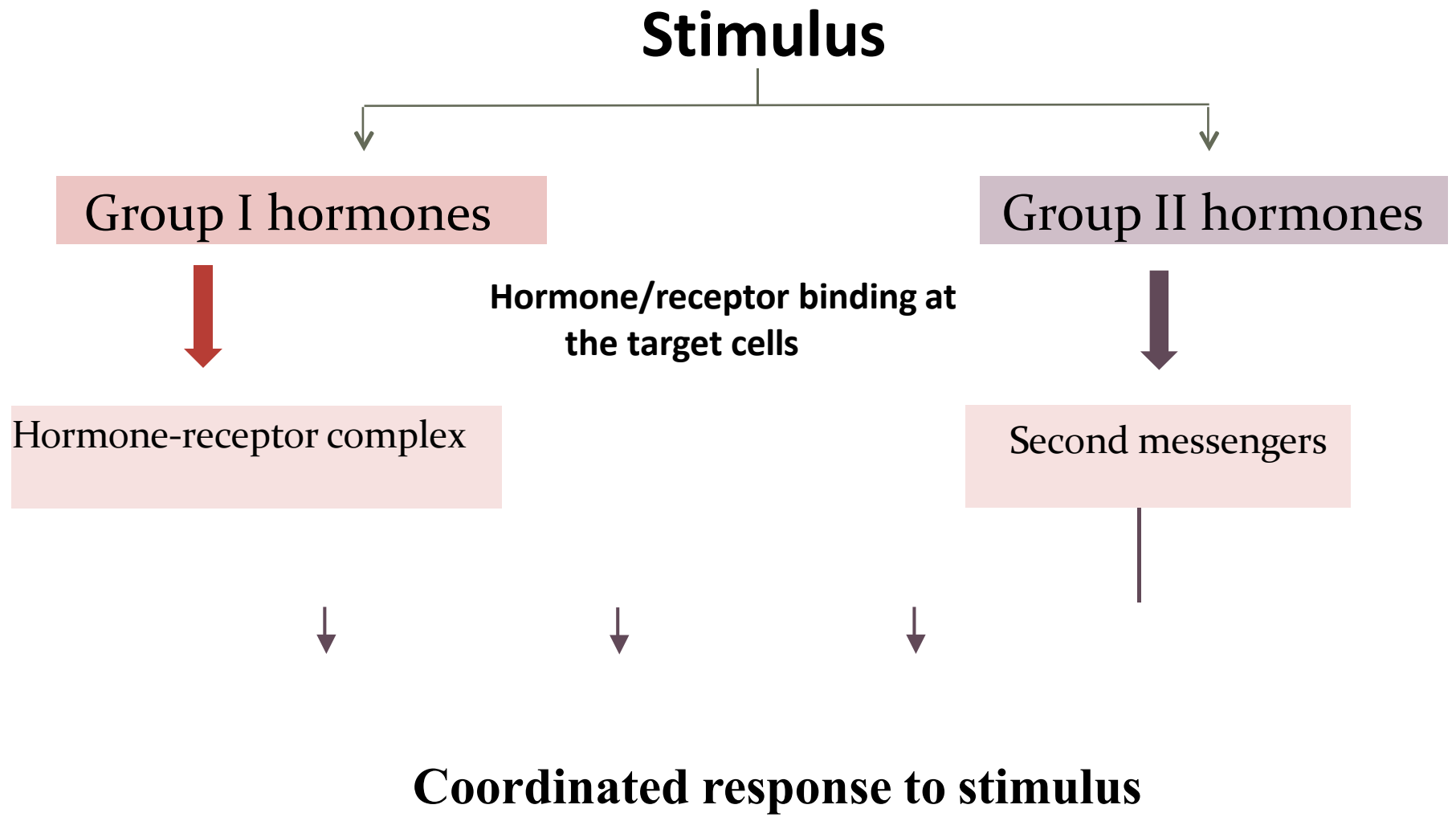
ASSISTANT PROFESSOR : SHIMAA ELSAYED

✓ ILOS

1. Define the signal transduction.
2. Classify the different types of hormones .
3. Differentiate the types of secondary messengers.
4. Understand the mechanism of action of protein hormones and growth factors.
5. Correlate the signal transduction with embryogenesis.

GENERAL FEATURES OF HORMONE CLASSES:





Classification of Hormones

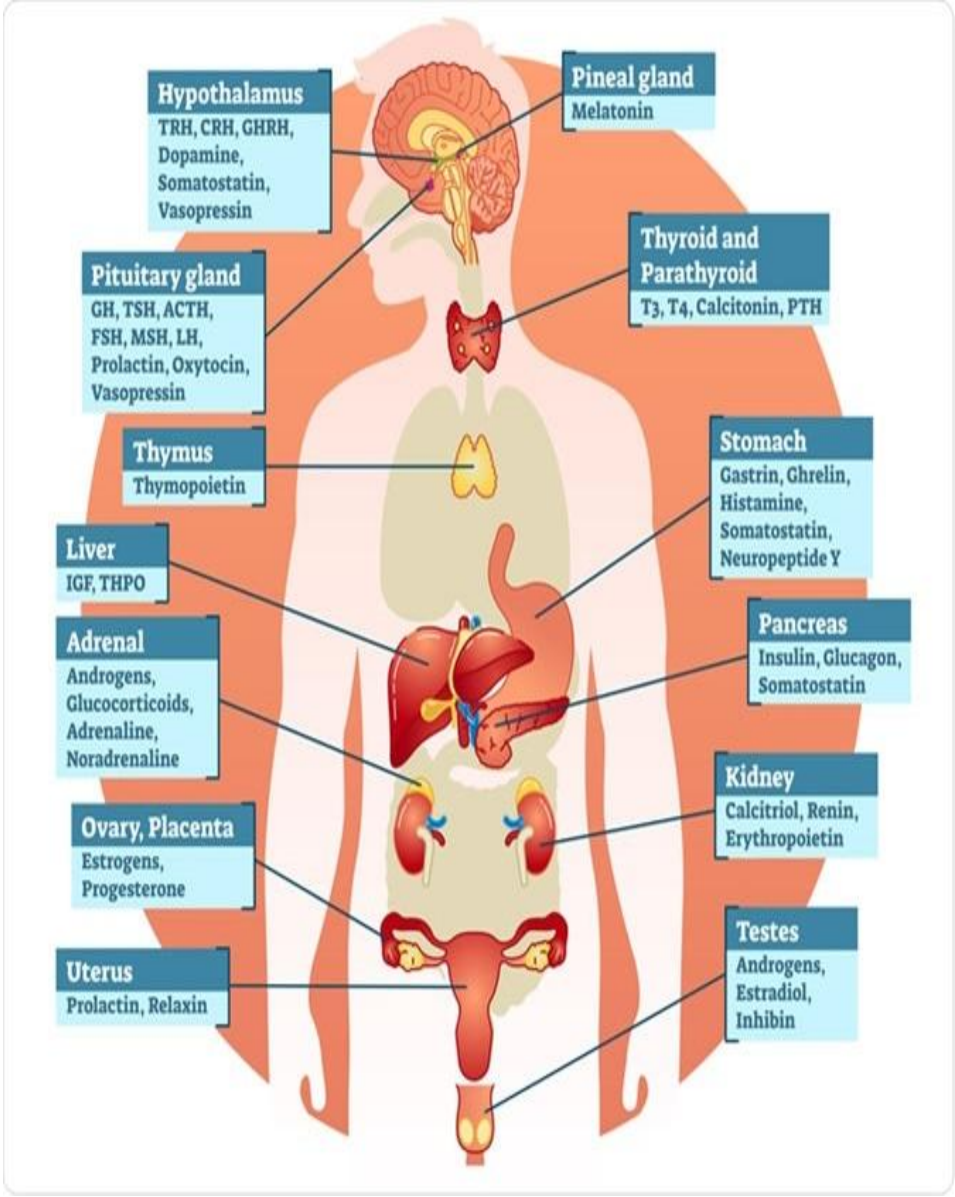
Hormones are classified

A. On the basis of mechanism of hormone action:

- Group I hormone
- Group II hormone

B. On the basis of chemical nature:

- Protein and peptide hormones (such as insulin, growth hormone, HCG, and embryonic signaling peptides like FGFs and TGF-β family members).
- Steroid hormone: Sex hormones, mineralocorticoids and glucocorticoids.
- Amino acids derivatives hormones: epinephrine, nor epinephrine (Catecholamines) etc.



	Group I	Group II
Types	• Steroids • Thyroid Hs (T3 & T4) • Calcitriol, retinoids	• Polypeptides • Glycoproteins • Catecholamines
Solubility	**Lipo**philic	**Hydro**philic.
Transport proteins	Yes	No
Plasma half-life	Long (hours – days) They're usually bound to proteins	Short (minutes)
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

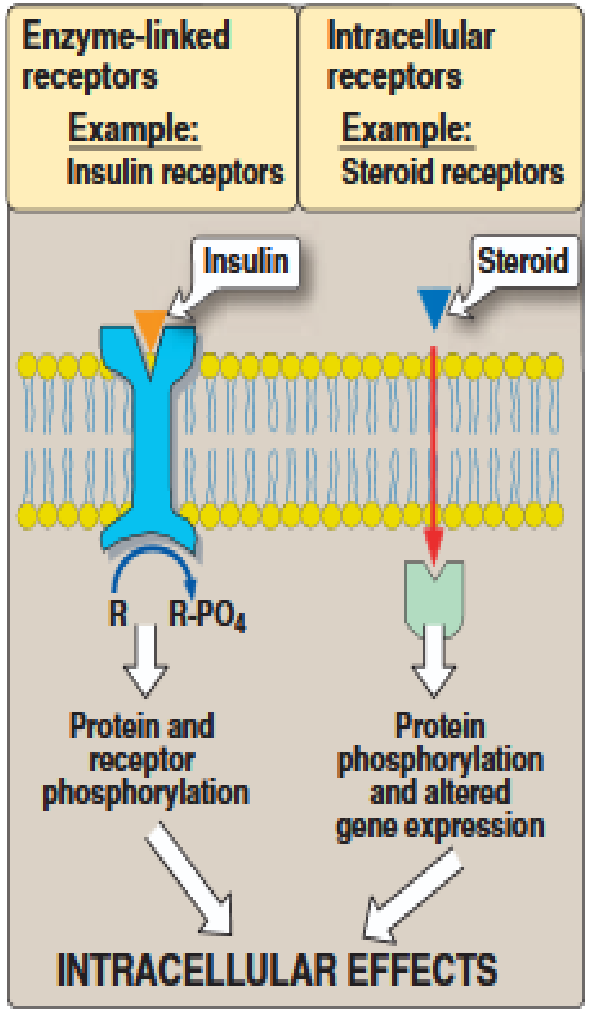


Table 44.1. Mechanism of action of hormones (for expansions for abbreviations, see Appendix No.I)

Group	Mechanism of action	Examples of hormone
I A	Hormones bind with cell surface receptors **with cAMP** as the second messenger	**ACTH**, ADH, FSH HCG, LH, TSH MSH, PTH, CRH Glucagon, Calcitonin Catecholamines Retinoic acid
I B	Hormones having cell surface receptors;**cGMP** as second messenger	**ANF** (atrial natriuretic factor), **NO** (nitric oxide)
I C	Hormones having cell surface receptors; second messenger is **calcium** or phosphatidyl inositol **(PIP_2)**	**TRH**, GnRH catecholamines Acetylcholine CCK, Gastrin Vasopressin Oxytocin, PDGF
I D	Hormones having cell surface rece-ptors and mediated through **tyrosine kinase**	**Insulin** Somatomedin EGF, FGF PDGF, CGSF NGF, IGF
I E	Hormones having cell surface receptors, but intracellular messenger is a kinase or utilize phosphatase cascade	**IL, GH, PRL, TNF,** Adiponectin, Leptin, Resistin, Erythropoietin
I I	Hormones that bind to **intracellular receptors**	**Glucocorticoids** Mineralocorticoids Estrogens, Progesterone Androgens Calcitriol, Thyroxine

Table 45.1. Major hypothalamic releasing factors

Name	Chemical nature	Biological actions
TRH; thyrotropin releasing hormone	Tripeptide; (pyro-Glu-His-Pro-NH_2)	Induces secretion of TSH and PRL; neuromodulator
GnRH; gonadotropin releasing hormone	Biologically active portion is a decapeptide	Releases LH and FSH; induces spermatogenesis, ovulation and testosterone
GHRH; growth hormone releasing hormone	37-44 amino acid; amino terminal end is tyrosine	Stimulates growth hormone secretion
CRF; corticotropin releasing factor	Amidated peptide with 41 amino acids	Release of ACTH. Inhibited by cortisol.
Somatostatin; growth hormone inhibitory factor	Cyclic peptide with 14 amino acids	Inhibits secretion of GH and TSH. Inhibits gut hormones, pancreatic and gastric secretion
PIF; prolactin inhibitory factor	Dopamine	Inhibits PRL release

Table 45.2. Hormones of anterior pituitary

Acronym	Full name	Chemical nature	Mol.wt. in kD	Amino acids
GH	Growth hormone	Polypeptide	22	191
ACTH	Adrenocorticotropic hormone	Polypeptide	4.5	39
LH	Luteinizing hormone	Glycoprotein; α,β chains	29	α = 89 β= 115
FSH	Follicle stimulating hormone	Glycoprotein; α,β chains	29	α = 89 β= 115
TSH	Thyroid stimulating hormone	Glycoprotein; α,β chains	28	α = 89 β= 114
α MSH	Melanocyte stimulating hormone	Polypeptide	13	
PRL	Prolactin	Polypeptide	22	198
	β Endorphins	Polypeptides	4	31
β LPH	β lipotropic hormone	Polypeptide	11	91

Classification of Hormones by Mechanism of Action

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

Group II. Hormones that bind to <u>cell surface receptors</u>

A. The second messenger is cAMP

❖ **Examples:**

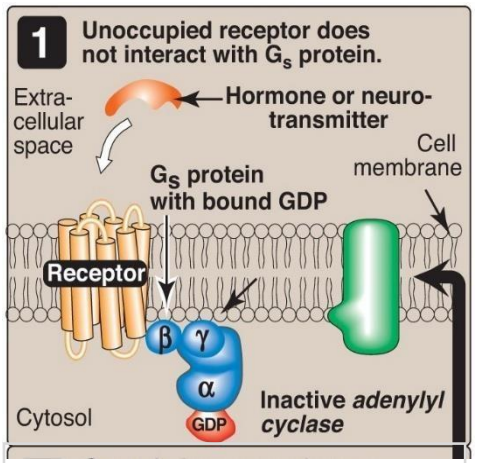
- ✓ **Catecholamines** (α_2-Adrenergic)
- ✓ **Catecholamines** (β-Adrenergic)
- ✓ **Ant. Pituitary:**

ACTH, FSH, LH & TSH

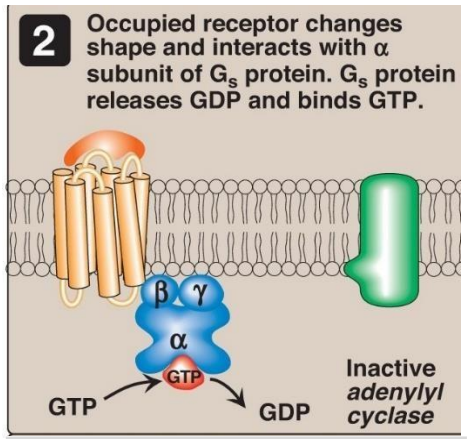
- ✓ **ADH** (Renal V**2**-receptor).
- ✓ **Calcitonin & PTH**
- ✓ **Glucagon**

Second Messenger system : cAMP

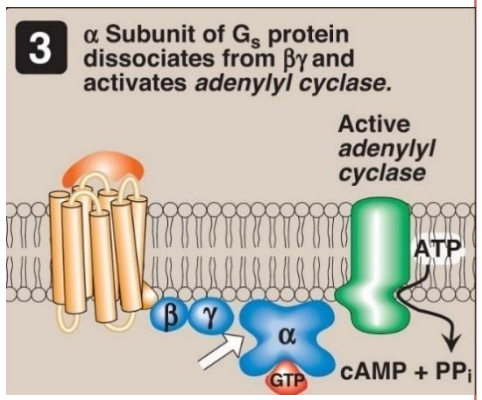
❖ **Mechanism:**



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



2- Replacement of 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.

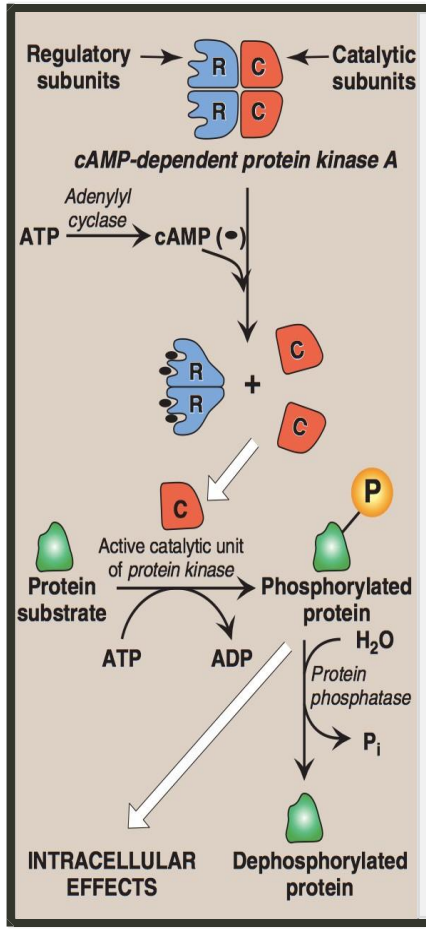
- **cAMP**
- **cGMP**
- **calcium or phosphatidyl-inositol (or both)**
- **tyrosine kinase cascade**

Classification of Hormones by Mechanism of Action

Group II. Hormones that bind to cell surface receptors

- cAMP
- cGMP
- calcium or phosphatidyl-inositol (or both)
- tyrosine kinase cascade

❖ Mechanism:



4- Activities of cAMP:

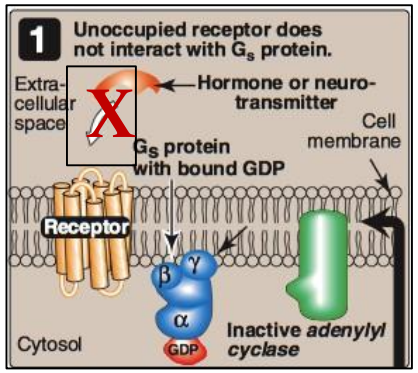
A. cAMP **activates** protein kinase A by binding to its regulatory subunits causing **the release of** 2 active catalytic subunits.

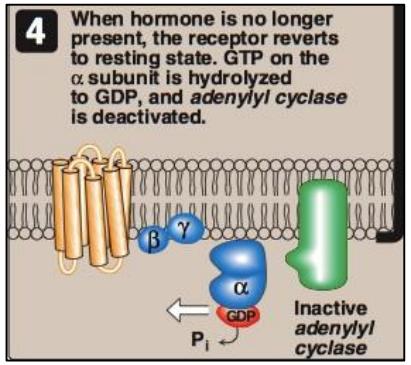
B. Theses active subunits **phosphorylate** the protein substrate by catalyzing the transfer of phosphate group from ATP to that protein.

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)

Classification of Hormones by Mechanism of Action

Group II. Hormones that bind to cell surface receptors

- cAMP
- cGMP
- calcium or phosphatidyl-inositol (or both)
- tyrosine kinase cascade

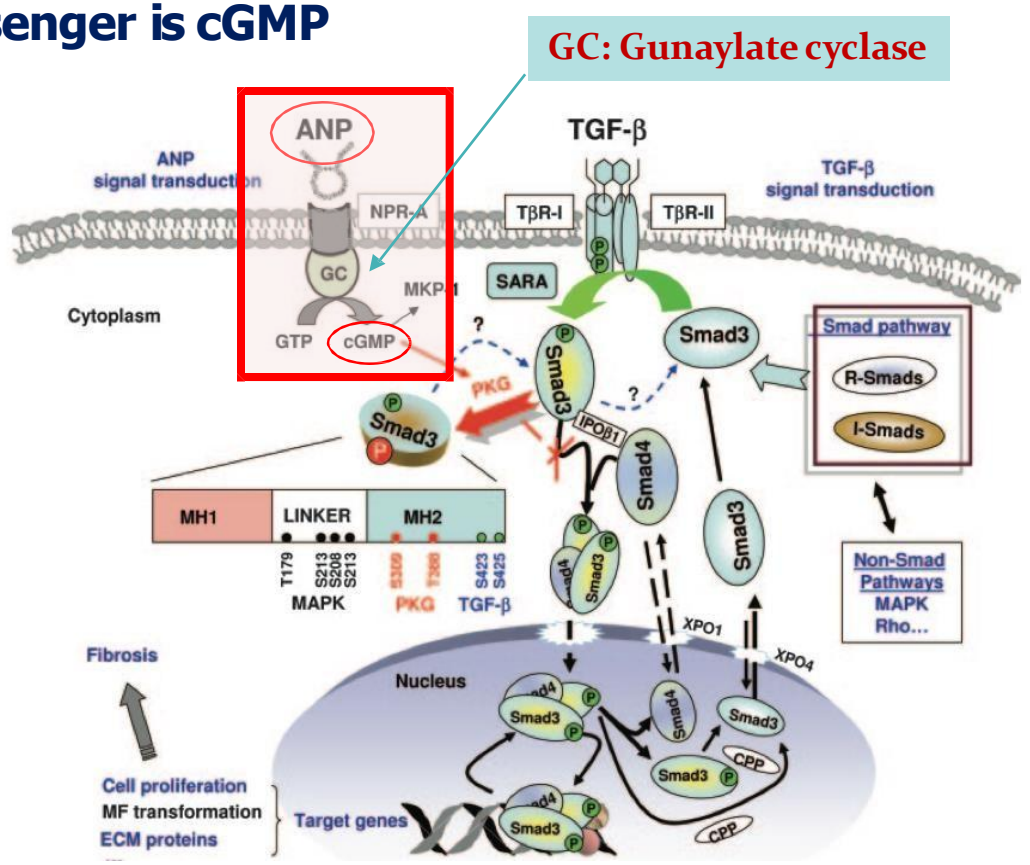
B. The second messenger is cGMP

❖ **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.



Classification of Hormones by Mechanism of Action

Group II. Hormones that bind to cell surface receptors

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

- ✓ **Acetylcholine** (muscarinic)
- ✓ **Catecholamines** (α1- Adrenergic)
- ✓ **Angiotensin II**
- ✓ **ADH** (vasopressin): **Extra**-renal V**1**-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.

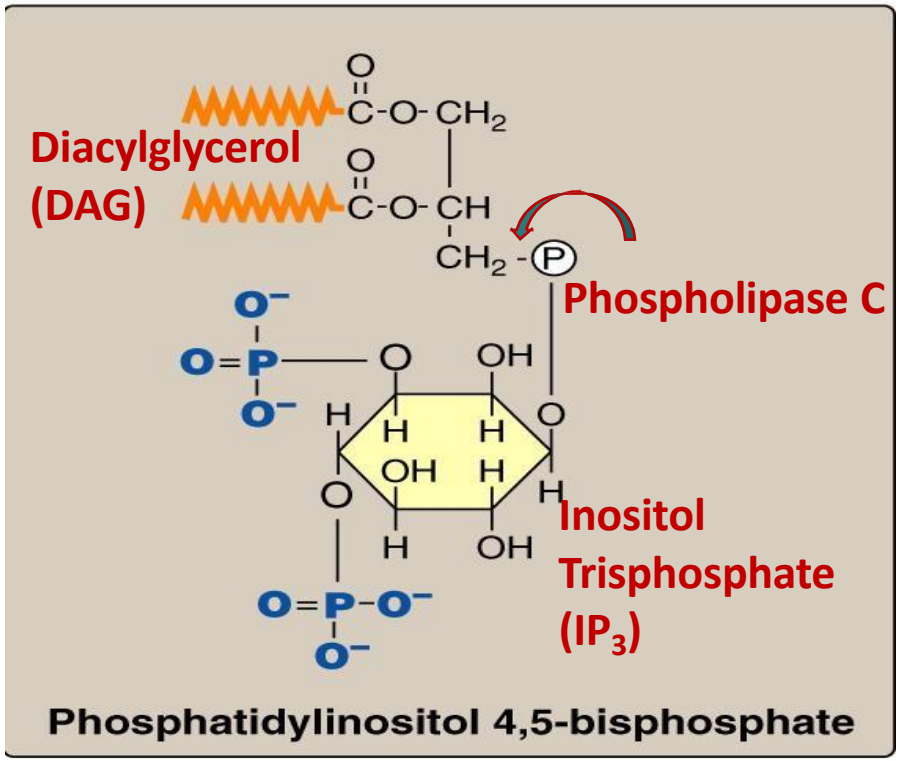
❖ **Calcium/Phosphatidylinositol (PI) System:**

- 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

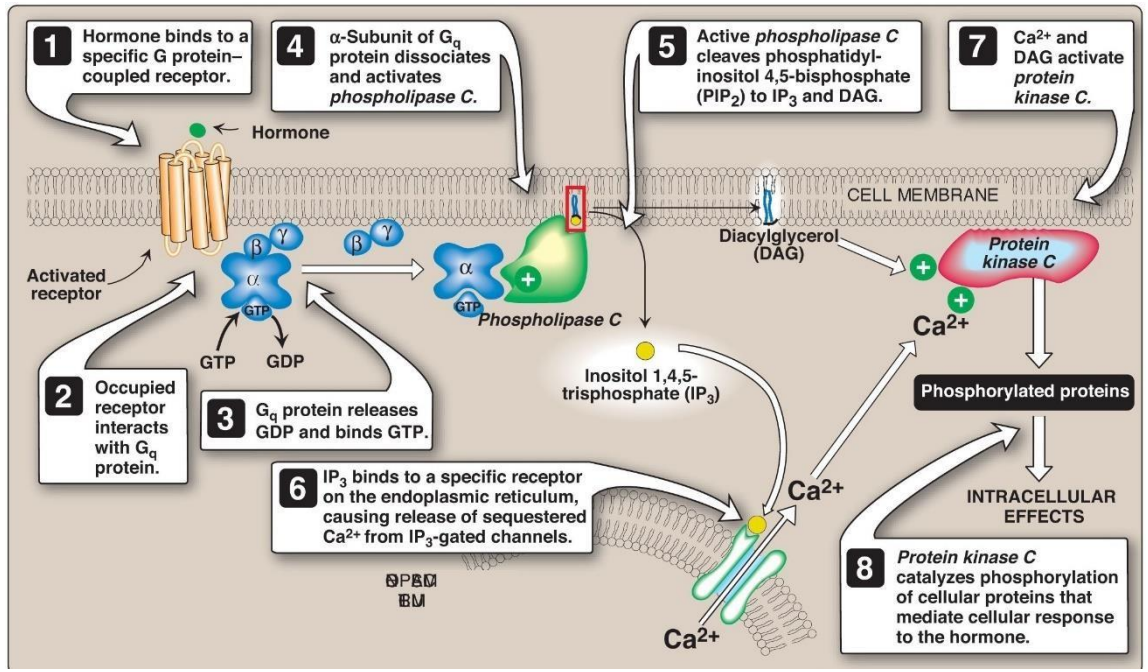
Classification of Hormones by Mechanism of Action

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

Group II. Hormones that bind to cell surface receptors

❖ 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 **βγ**-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.



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

- cAMP
- cGMP
- calcium or phosphatidyl-inositol (or both)
- tyrosine kinase cascade

Classification of Hormones by Mechanism of Action

Group II. Hormones that bind to cell surface receptors

- cAMP
- cGMP
- calcium or phosphatidyl-inositol (or both)
- **tyrosine kinase cascade**

D. The second messenger is a tyrosine kinase cascade

Examples:

- ✓ GH & Prolactin
- ✓ Insulin
- ✓ Erythropoietin

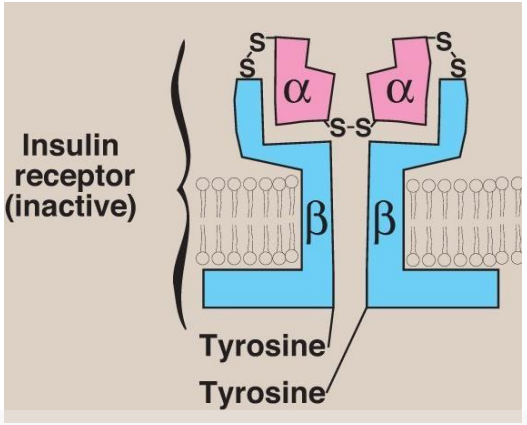
Biologic Effects of Insulin:

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

Decrease:
- Gluconeogenesis.
- Glycogenolysis.
- Lipolysis.

+ Altered gene expression

Insulin receptor:



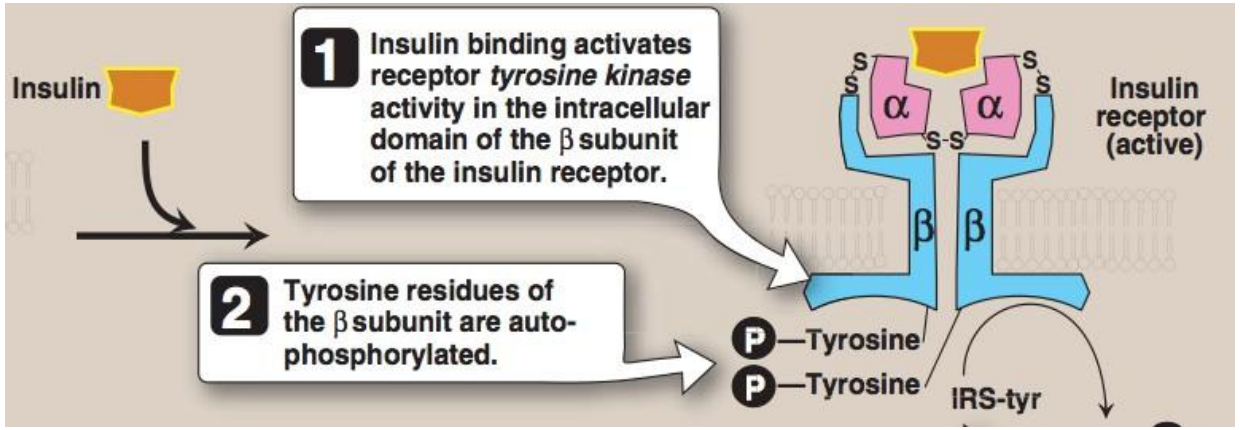
Insulin receptor is a **dimer** that consists of 2 identical units.
Each unit has:
***An alpha-chains:** on the **outside** and create **a binding site** for insulin.
***A beta-chains:** **Spans the plasma membrane** and its cytosolic domain is a **tyrosine kinase**.
Subunits are bound together by disulfide bond.

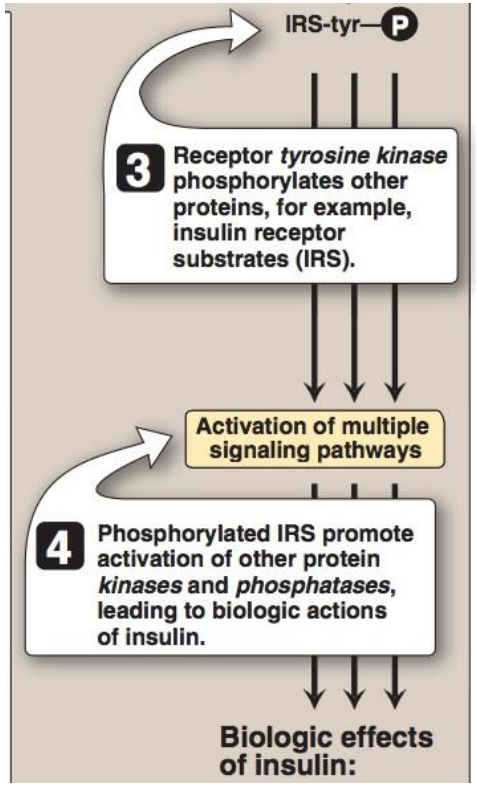
Classification of Hormones by Mechanism of Action

Group II. Hormones that bind to cell surface receptors

- cAMP
- cGMP
- calcium or phosphatidyl-inositol (or both)
- tyrosine kinase cascade

❖ Mechanism of Insulin action:



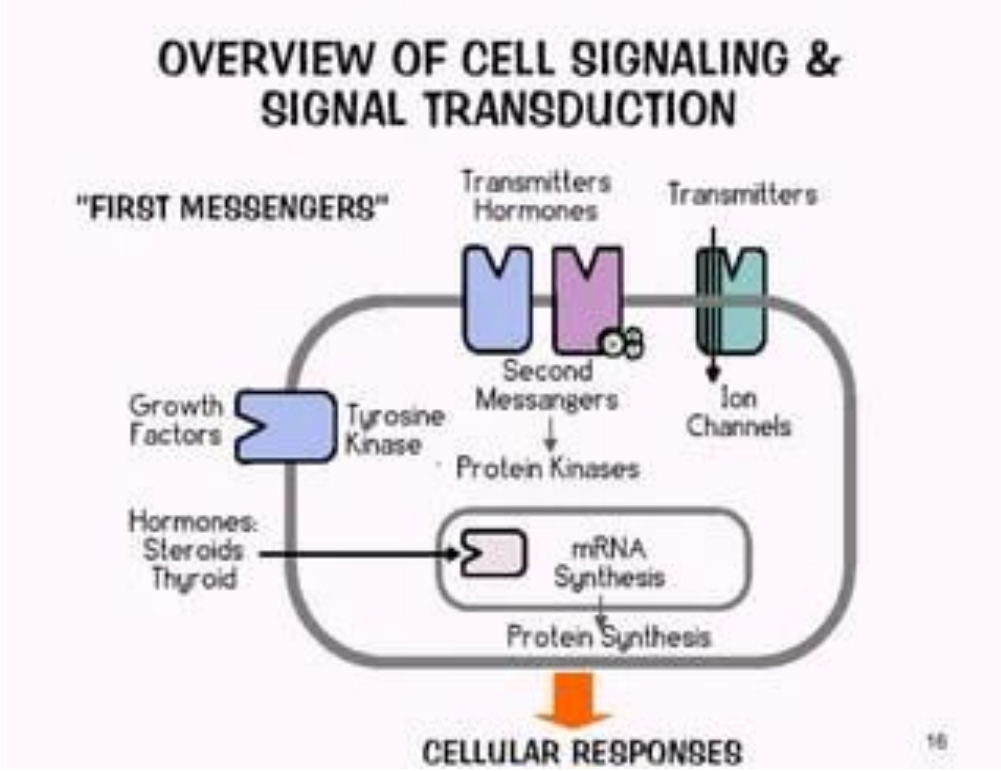


Binding of insulin to the alpha-subunit → **conformational changes** that are transmitted to β -subunit → Rapid **autophosphorlation** of tyrosine residues of the β -subunits → Then **phosphorylation of** *insulin receptor substrates* (IRS) "a family of proteins" by tyrosine kinase → **Activation** of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

Insulin Signal Transduction Pathway

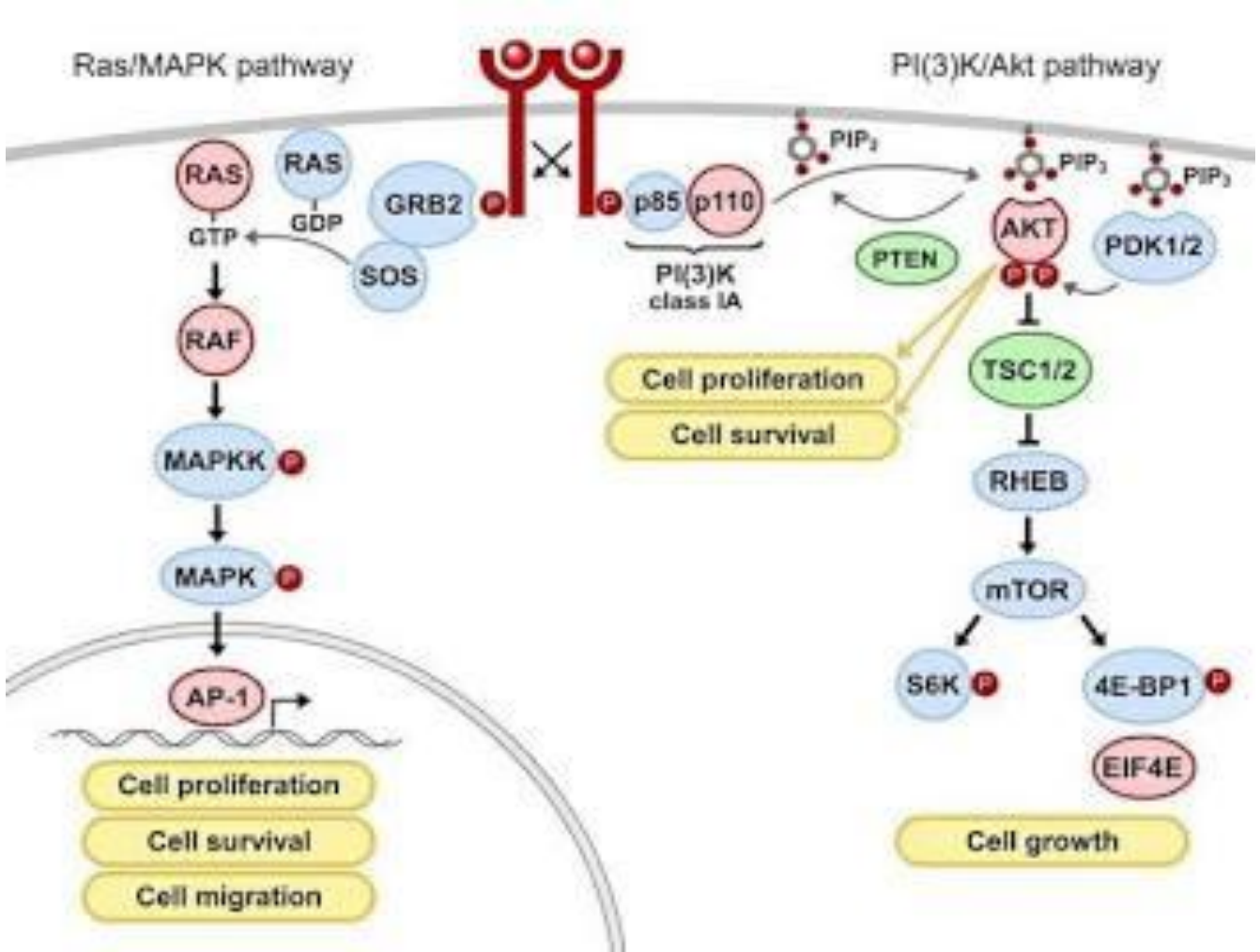
Protein and peptide hormones (such as insulin, growth hormone, HCG, and embryonic signaling peptides like FGFs and TGF-β family members) operate through cell-surface receptor signaling pathways to orchestrate embryonic development, cellular differentiation, and organogenesis.

- **The growth factors generally cause mitosis or differentiation of target cells. These may be considered as local hormones.**



Signaling Factor / Hormone	Primary Receptor System	Role in Embryonic Development	Organogenesis Impact
Fibroblast Growth Factors (FGFs)	Receptor Tyrosine Kinase (RTK) →MAPK Pathway	Mesoderm induction, limb bud outgrowth, primitive streak formation	Heart tube formation, lung branching morphogenesis, limb development
Transforming Growth Factor-β / Nodal / BMPs	Serine/Threonine Kinase Receptors →Smad Pathway	Left-right axis determination, dorsal-ventral patterning, gastrulation	Bone/cartilage development, kidney induction, vascular formation
Human Chorionic Gonadotropin (hCG)	GPCR →Adenylate Cyclase / cAMP/ PKA Pathway	Maintenance of the corpus luteum, stimulation of progesterone production	Implantation support, maternal-fetal crosstalk, placental angiogenesis
Insulin-like Growth Factors (IGF-1, IGF-2)	RTK →PI3K / Akt Pathway	Embryonic cell proliferation, tissue growth, inhibition of apoptosis	Overall embryonic body size, muscular development, skeletal maturation
Growth Hormone (GH) & Prolactin	JAK / STAT Pathway	Fetal growth regulation, metabolic priming	Organ maturation during late-stage gestation

When extracellular FGF ligands bind to transmembrane FGF receptors (FGFRs, primarily FGFR1 in the mesenchyme), a multi-step intracellular phosphorylation cascade is triggered.



https://www.youtube.com/watch?v=TgNwxF3aQpE&pp=ygUqbWVjYWhpbnNtIG9mIGFjdGlvbiBvZiBob3Jtb25lcyBhbmltYXRpb24g

- **References : Textbook of Biochemistry for Medical Students,2011, DM Vasudevan, Sreekumari S, Kannan Vaidyanathan, ISBN: 978-93-5025-016-7.Chapters:44,45 (P520-531).**