جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

General Mechanisms of The Action of Hormones

Biochemistry Team 437

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Highlights

Endocrine block

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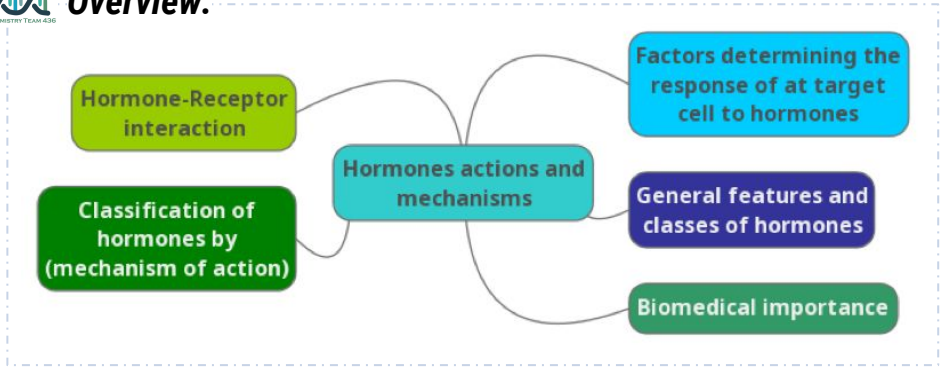
Objectives:

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

Overview:



Outline:

- 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**[1] 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[2]
- A **target**[3] is any cell in which the hormone (ligand) binds to its receptor to start the action

1: response of the target cell
2: e.g. insulin has different effects in muscles and hepatocytes
3: Target cell: cell that has the specific receptor for the hormone

Some Terms:
- Stimulus : environmental change
- Hormone / ligand : signal
- Receptor: Recognise the signal, present on the cell surface or inside the cell

- 1,2,3 are hormone related
- 4,5 are receptor relate

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5- The number, relative activity, and state of occupancy of the specific receptors[3]

1- The rate of synthesis & secretion of the hormone[1]

Factors determining the response of a target cell to a hormone

4- Post-receptor factors[4]

2- The conversion of inactive form of the hormone to its active form[2]

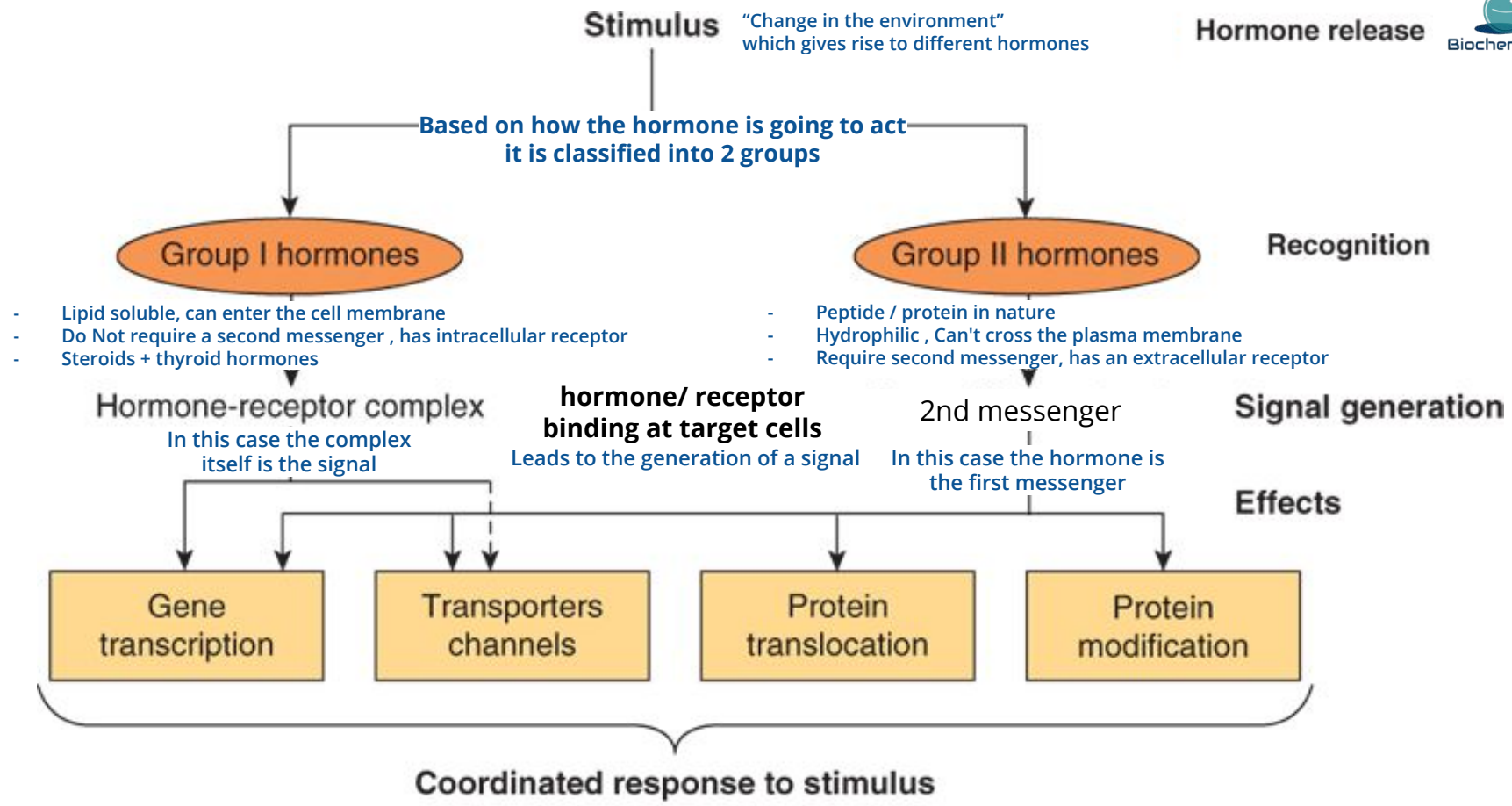
3- The rate of hormone clearance from plasma (half-life & excretion)

1: It's controlled by 3 factors
- Stimulant that increase its synthesis
- The healthy of gland to produce hormone
- The presence of precursor that makes hormone

2: e.g: insulin is first secreted ase preproinsulin → proinsulin → insulin "active" If it remain in inactive form it will be worthless

3: Either the receptor is present or absent or free or occupied by drugs

4: examples are: **second messengers**, gene transcription machinery.



Important!

General Features of Hormone Classes

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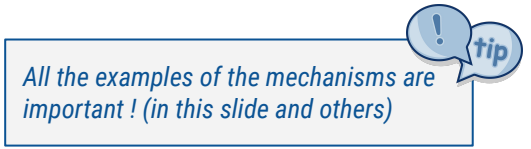
	Group I	Group II
Types	Steroids Thyroid Hs (T3 & T4) Calcitriol (vitamin D) , retinoids (retinoic acid form of vitamin A)	Polypeptides Glycoproteins Catecholamines (fight and flight hormones e.g. epinephrine & norepinephrine)
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes (maily albumin)	No
Plasma half-life	Long (hours – days)	Short (minutes)
Receptor	Intracellular inside cell "cytosolic or nuclear"	Plasma membrane (on the plasma membrane)
Mediator	Receptor-hormone complex (direct)	2nd messengers(indirect): 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):

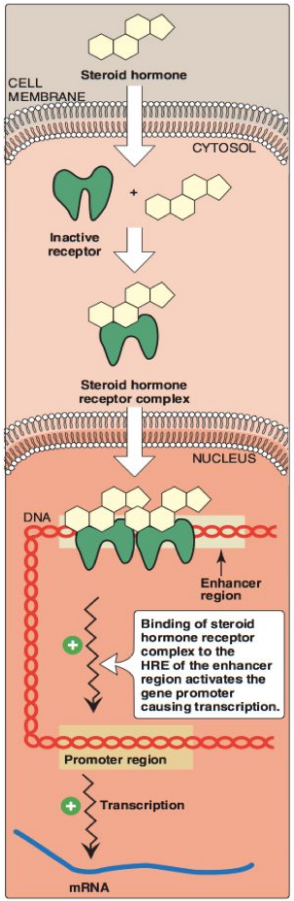
- Steroid hormones
- Thyroid Hormones (T_3 & T_4)
- Calcitriol (active form of vitamin D, 1,25$[OH]_2$-D_3)
- Retinoic acid

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 (vitamin A)

Team 436 Explanation

Steroid hormone is bound to albumin in the plasma → it crosses the cell membrane where it will bind to its inactive receptor (steroid hormone receptor complex) → when the complex crosses to the nucleus it binds to Hormone Response Element (HRE) which is present in the enhancer region and it affects the promoter region to change the transcription and protein synthesis of the gene.



Classification of Hormones by Mechanism of Action

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You have to memorize all the mechanisms and know which hormone acts by which second messenger.

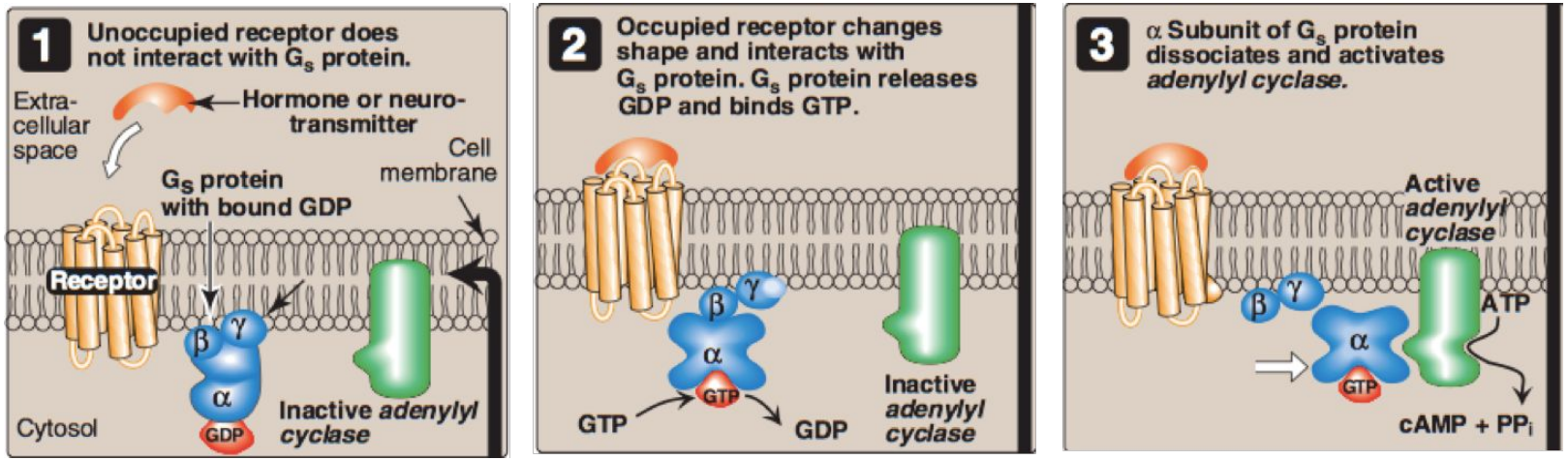
II. Hormones that bind to cell surface receptors
A. The second messenger is cAMP

- Catecholamines (α_2- Adrenergic)
- Catecholamines (b- Adrenergic)
- Ant. Pituitary: ACTH, FSH, LH & TSH
- ADH (Renal V2-receptor 1) Antidiuretic Hormone
- Calcitonin & PTH (work to maintain the calcium levels)
- **Glucagon**

Be mindful:

- **A_2 and b Adrenergic catecholamines have cAMP as their 2nd messenger, whereas α_1 has calcium and IP3**
- **There are two types of ADH receptors:**
  - **V2: renal, cAMP**
  - **V1: extra renal, calcium and IP3**

Cascade for Formation of cAMP by cell-surface Hormones



- Hormones which will act by cAMP or cGMP are G protein coupled receptors
- Our unoccupied receptor is coupled to a trimeric G protein "3 subunits, alpha beta and gamma" & bound to a GDP (inactive) → when the hormone binds to the receptor it causes a conformational change in the receptor → the alpha subunit detaches from the beta & gamma and GDP is replaced by GTP → activates the adenylyl cyclase → produces cAMP from ATP
- There are many types of G protein like G s which is stimulatory and G i which is inhibitory

1. Ligand (hormone) binds to receptor which will react with Gs and activate G protein
2. The active form of G protein is G a (alfa) subunit
3. This active form will activate adenylyl cyclase and this activation will convert ATP to CAMP

Important!

Actions of cAMP

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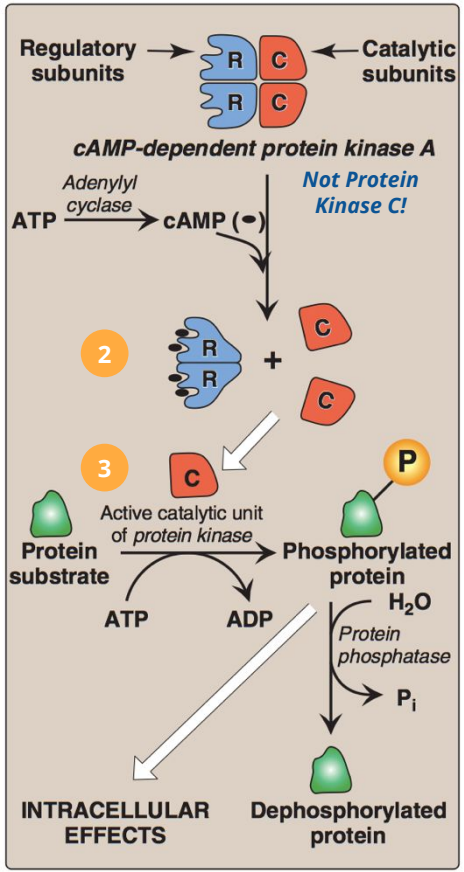


1

- **A**denylyl cyclase produced c**A**MP which activate protein kinase **A**
- **G**uanylyl cyclase produced c**G**MP which activate protein kinase **G**

cAMP activates protein kinase A. follow the image :

1) Protein kinase A has 2 regulatory subunits and 2 catalytic subunits. The regulatory subunits cover the active sites of the catalytic subunits, and the enzyme cannot do any catalysis
2) To make this enzyme active, you have to remove the regulatory subunit which can be done by cAMP.
3) Active catalytic subunits bind to protein substrates and phosphorylate them (add phosphate group).

4

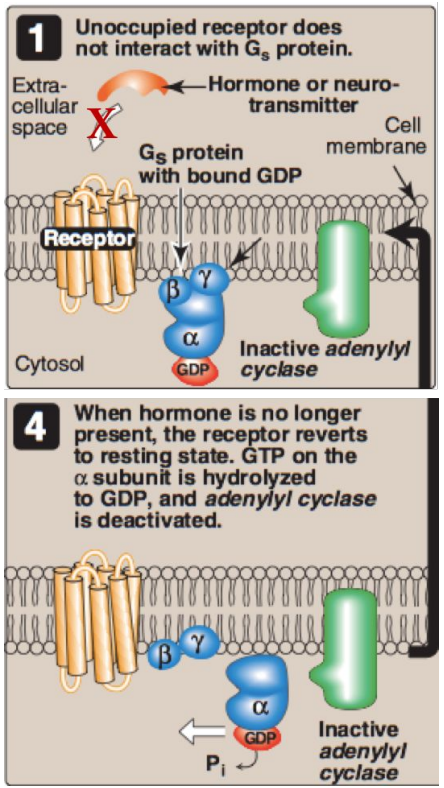
4) Phosphorylated proteins are translated to intracellular effect.

5

5) Protein phosphatase is the enzyme that stops the intracellular effect if we don't need it anymore by dephosphorylating the proteins

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[1]
5. Hydrolysis of GTP into GDP[2]
6. Binding of α-subunit to βγ-subunits
7. Inactivation of adenylyl cyclase



-Phosphorylation of **protein kinase A** occurs on the hydroxyl groups of **Serine**, **Threonine** residues in a protein
1- protein kinase A is cAMP dependant
2: can be done by the alpha subunit itself

Classification of Hormones by Mechanism of Action

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II. Hormones that bind to cell surface receptors
B. The second messenger is cGMP

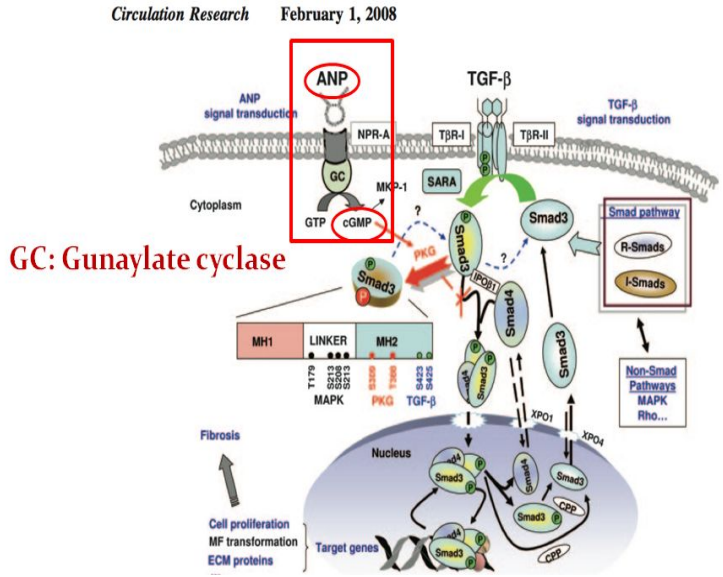
- Atrial natriuretic peptide **(ANP)**
- **Nitric oxide**

- ANP is released in response to stretching of the cardiac muscle due to volume overload
- It functions to reduce the rate of synthesis of collagen → decreases fibrosis

Pathway:

- ANP binds to NPR receptor → GC protein activation → conversion of GTP to cGMP
- cGMP activates protein kinase G which phosphorylate SMAD3
- Normally, non phosphorylated SMAD3 binds to SMAD4 and upregulate collagen synthesis and fibrosis. But when it is phosphorylated, it can't bind to SMAD4 so collagen synthesis and fibrosis rate goes down.

Atrial Natriuretic Peptide (ANP)



GC: Gunaylate cyclase

Difference between cAMP & cGMP pathways:

- Guanylate cyclase (GC) instead of Adenylyl cyclase
- No α-β subunits (GC binds directly to receptors)

Differences between cAMP and cGMP

cAMP	cGMP
G protein is not bound to the receptor	G protein is bound to receptor
Adenylyl cyclase	Guanylate cyclase (GC)
Adenylyl cyclase is not attached to the receptor	Guanylate cyclase is attached to the receptor
α-β subunits are present	No α-β subunits
ATP is converted to cAMP	GTP is converted to cGMP

Classification of Hormones by Mechanism of Action

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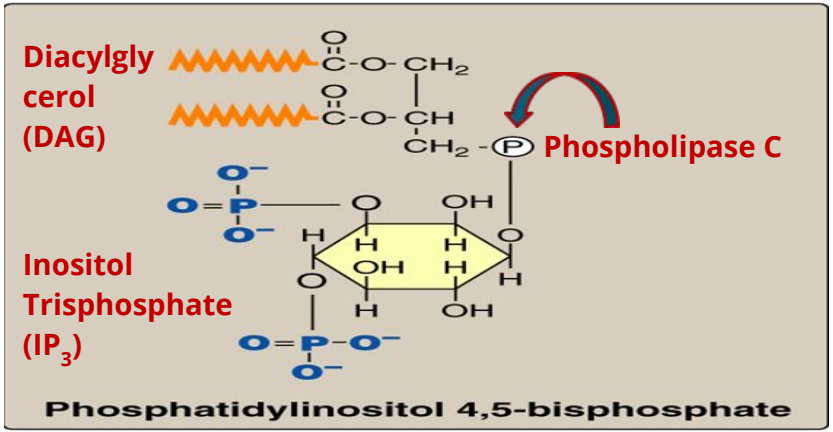
II. Hormones that bind to cell surface receptors
C. The second messenger is <u>calcium or phosphatidylinositol (or both)</u>

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

Calcium/Phosphatidylinositol System

Phosphatidylinositol bisphosphate "PIP2" is a membrane phospholipid that can be phosphorylated "by **phospholipase C*** into IP3 "inositol trisphosphate"

- Pathway is in the next slide



Don't skip the picture!

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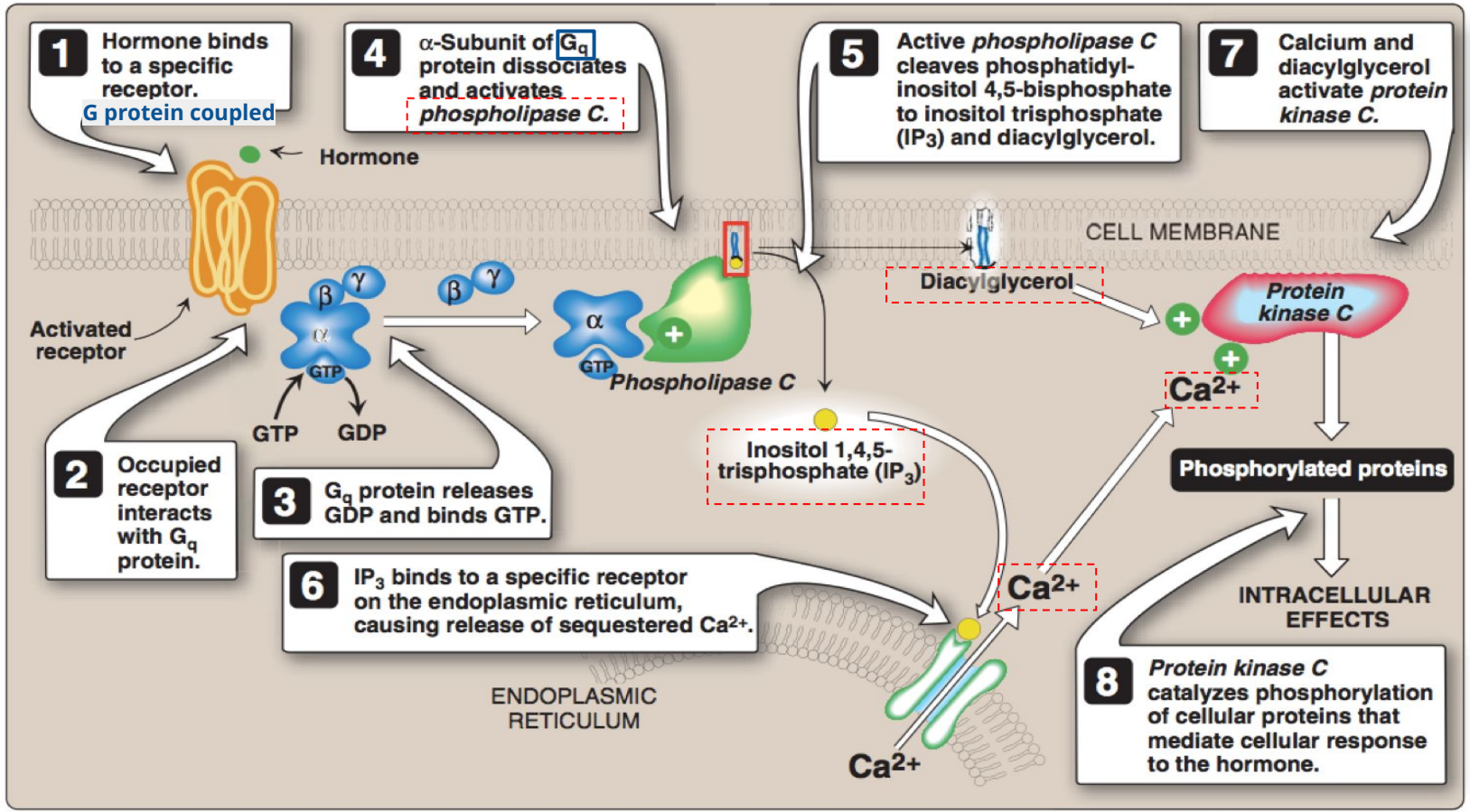

Classification of Hormones by Mechanism of Action

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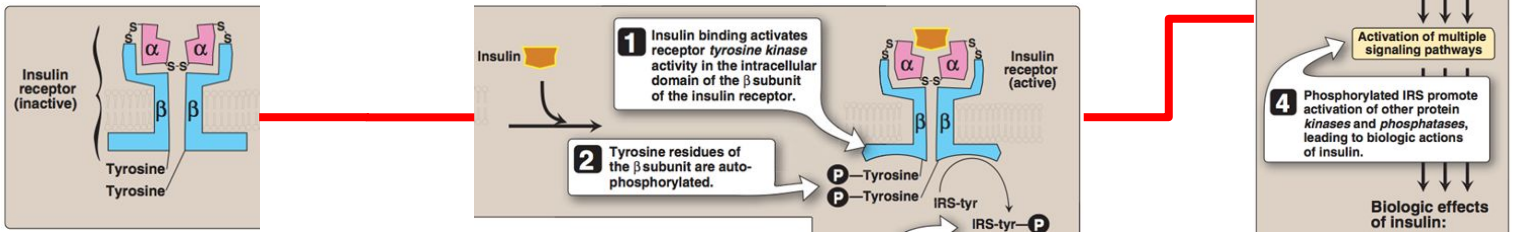
II. Hormones that bind to cell surface receptors
D. The second messenger is a tyrosine kinase cascade

- GH & Prolactin
- Insulin
- Erythropoietin

Don't skip the pictures!

- Kinase: responsible for phosphorylating proteins
- Tyrosine kinase: phosphorylates tyrosine

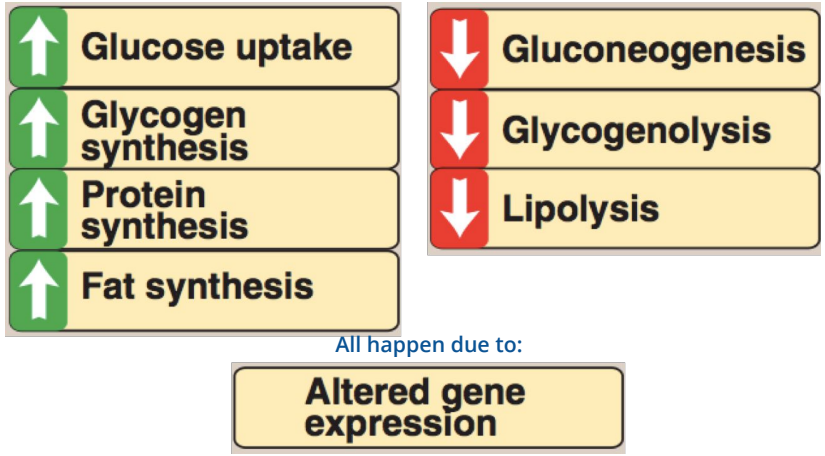
Mechanism of Insulin action



- Two αβ dimers "subunits" make the tetramer receptor
- Alpha is outside the cell membrane "where insulin binds"
- Beta has an intramembranous and intra cytosolic part

- When insulin binds to the receptor, it activates the receptor by causing conformational changes the brings the two subuints together "dimerization"
- The activated beta subunit has 2 kinase activities:
  - Autophosphorylation of tyrosine within the beta subunit
  - phosphorylation of the target proteins, mainly IRS "insulin receptor substrates", which in turn phosphorylates other proteins leading to the action of insulin "next slide"

Biologic Effects of Insulin



Biomedical Importance

- Excessive (e.g.,hyperthyroidism, Cushing)
- Deficient (e.g., hypothyroidism, Addison)
- 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*)

*Mainly causes increase in ADH secretion, which leads to excessive water retention that is perceived as hyponatremia.

Take Home Messages

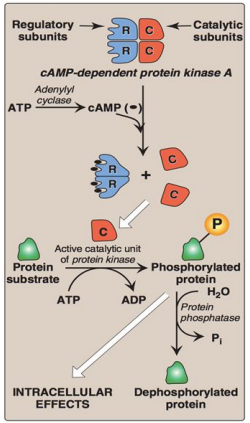
- Hormones are involved in responses to a stimulus, using a variety of signaling mechanisms to facilitate cellular adaptive responses.
- Group I hormones are lipophilic, while group II are hydrophilic. Other differences exist between both groups.
- Hormones can be classified according to their mechanism of action *(specific examples of each category were discussed)*
- Biomedically, studying hormones' actions in details helps to:
- Understand consequences of abnormal hormone release-related diseases (excessive, deficient or inappropriate)
- Design therapeutic approach for such diseases.

Summary

General Features of Hormone Classes		
	Group I	**Group II**
Types	Steroids Thyroid Hs (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

Summary

Classification of Hormones by Mechanism of Action

Types	Subtypes	Examples	Mechanism	Other
I. 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	1-steroid hormone cross the plasma membrane into the cytosol 2-In the cytosol it binds to a specific cytosolic or nuclear receptor and forms receptor ligand complex 3-the complex goes inside the nucleus and binds to **HRE (hormone response element)** which is a specific regulatory DNA sequences 4-this is causes increase of the transcription so the rate of the protein synthesize increases as well	-
II. Hormones that bind to cell surface receptors	A. The second messenger is cAMP Adenylyl cyclase = cAMP	Catecholamines (α2- Adrenergic). Catecholamines (b- Adrenergic). Ant. Pituitary: ACTH, FSH, LH & TSH. ADH (Renal V2-receptor). Calcitonin & PTH. Glucagon.	1-Binding of ligand "Hormone" causes a conformational change in the receptor 2-Replacement of of the GDP of the G protein(S) "α subunit" with GTP. 3-GTP-bound form of the alpha subunit dissociates from the beta and gamma subunits and move to adenylyl cyclase "AC" and activate it. 4-ATP will be converted to cAMP which will activate protein kinase A	Actions of cAMP : 
	B. The second messenger is cGMP Guanylate cyclase = cGMP	Atrial natriuretic peptide (ANP). Nitric oxide (NO).	1- ANP binds to it's receptor which is associated with the enzyme guanylate cyclase(GC) 2- GC converts GTP into cGMP 3- The cGMP activate the enzyme protein kinase G	

Summary

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Classification of Hormones by Mechanism of Action

Types	Subtypes	Examples	Mechanism	Other	
II. Hormones that bind to cell surface receptors	C. The second messenger is calcium or phosphatidylinositol (or both) Phospholipase C = IP3	Acetylcholine (muscarinic). Catecholamines (α1-Adrenergic). Angiotensin II. ADH (vasopressin): ExtrarenalV1-receptor.	1- Hormone binds to G-protein coupled receptor. 2- Receptor Interacts with G protein(q) Which releases GDP and binds with GTP. 3. α subunit dissociates from βγ- subunits, and activates Phospholipase C. 4. Phospholipase cleaves phosphatidylinositol 4,5-bisphosphate to DAG and IP3 5. IP3 binds to a specific receptor on RER causing release of Ca. 6. Calcium and DAG synergistically activate protein kinase C . 7. Protein kinase C catalyzes protein phosphorylation.	-	
	D. The second messenger is a tyrosine kinase cascade	GH & Prolactin. Insulin. Erythropoietin.	Insulin receptor is a dimer that consists of 2 identical units. 1-Insulin binding activates receptor tyrosine kinase of Beta Subunit. 2-phosphorylation of tyrosine. 3-receptor tyrosine kinase phosphorylates other proteins like IRS. 4-IRS activates other proteins and lead to the biological action.	Biologic Effects of Insulin	
				Increase	**Decrease**
				1- Glucose up take 2- Glycogen synthesis 3-Protein synthesis 4- Fat synthesis	1-Gluconeogenesis. 2-Glycogenolysis. 3-Lipolysis.

	Group I	Group II			
Receptor	**intracellular**	**Binds to the surface**			
2nd messenger	Receptor intracellular	cAMB	cGMP	Ca+ & phosphatdylinositol	Tyrosine kinase
Examples	1. Steroids (Sex hormones) 2. Thyroid hormones T3 ,T4 & calcitriol	1. Catecholamine 2. Anterior pituitary hormones (ACTH, FSH, LH, TSH)	1. Atrial natriurec peptide 2. nitric oxide	1. Acetylcholine 2. α1-adrenergic 3. angiotensin II	1. GH, prolactin 2. insulin 3. erythropoietin

MCQs:

1- Which of the followings are considered as hydrophilic hormone?

A. Estrogen
B. Aldosterone
C. Epinephrine

2- When ADH binds to its extra renal V1 receptor, its second messenger will be?

A. Ca/Phosphatidylinositol
B. cAMP
C. cGMP
D. Tyrosine kinase

3- Glycogenolysis is decreased by?

A. Glucagon
B. Insulin
C. Epinephrine
D. cAMP

4- Which one of the following hormones uses tyrosine kinase cascade as a second messenger?

A. Prolactin
B. ADH
C. Acetylcholine
D. Glutaminase

4-A
3-B
2-A
1-C

Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

- طارق العميم
- محمد الصويغ
- نايف المطيري
- سلطان الناصر
- صالح الوكيل
- نواف اللويمي
- عبدالملك الشرهان

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