Biochemistry Bandits 434

MED 434

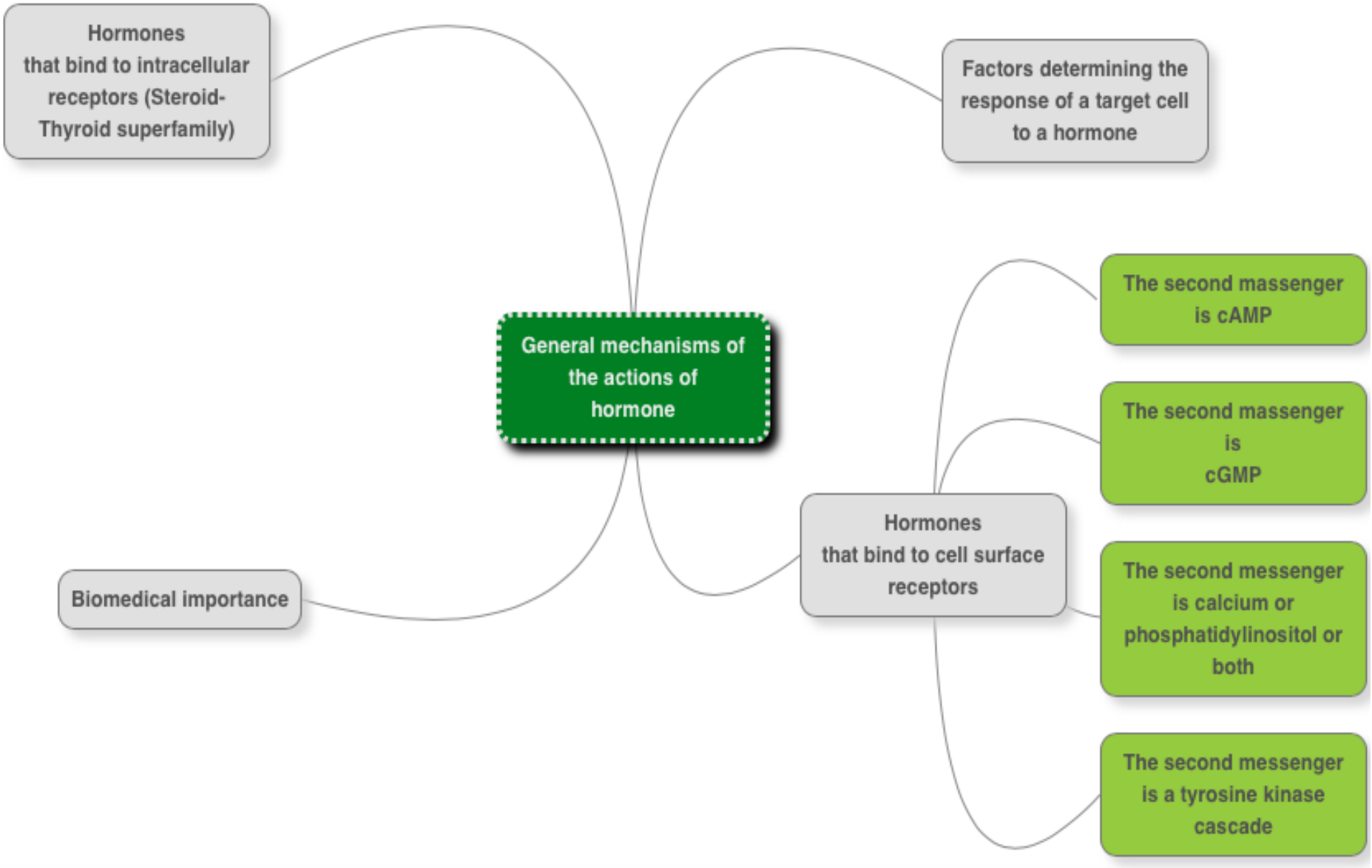
GENERAL MECHANISMS OF THE ACTIONS OF HORMONE

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.

❖ **Important** ❖ Extra ❖ Biochemistry Edit

MIND MAP


Hormones that bind to intracellular receptors (Steroid-Thyroid superfamily)
Factors determining the response of a target cell to a hormone
General mechanisms of the actions of hormone
The second massenger is cAMP
The second massenger is cGMP
Hormones that bind to cell surface receptors
Biomedical importance
The second messenger is calcium or phosphatidylinositol or both
The second messenger is a tyrosine kinase cascade

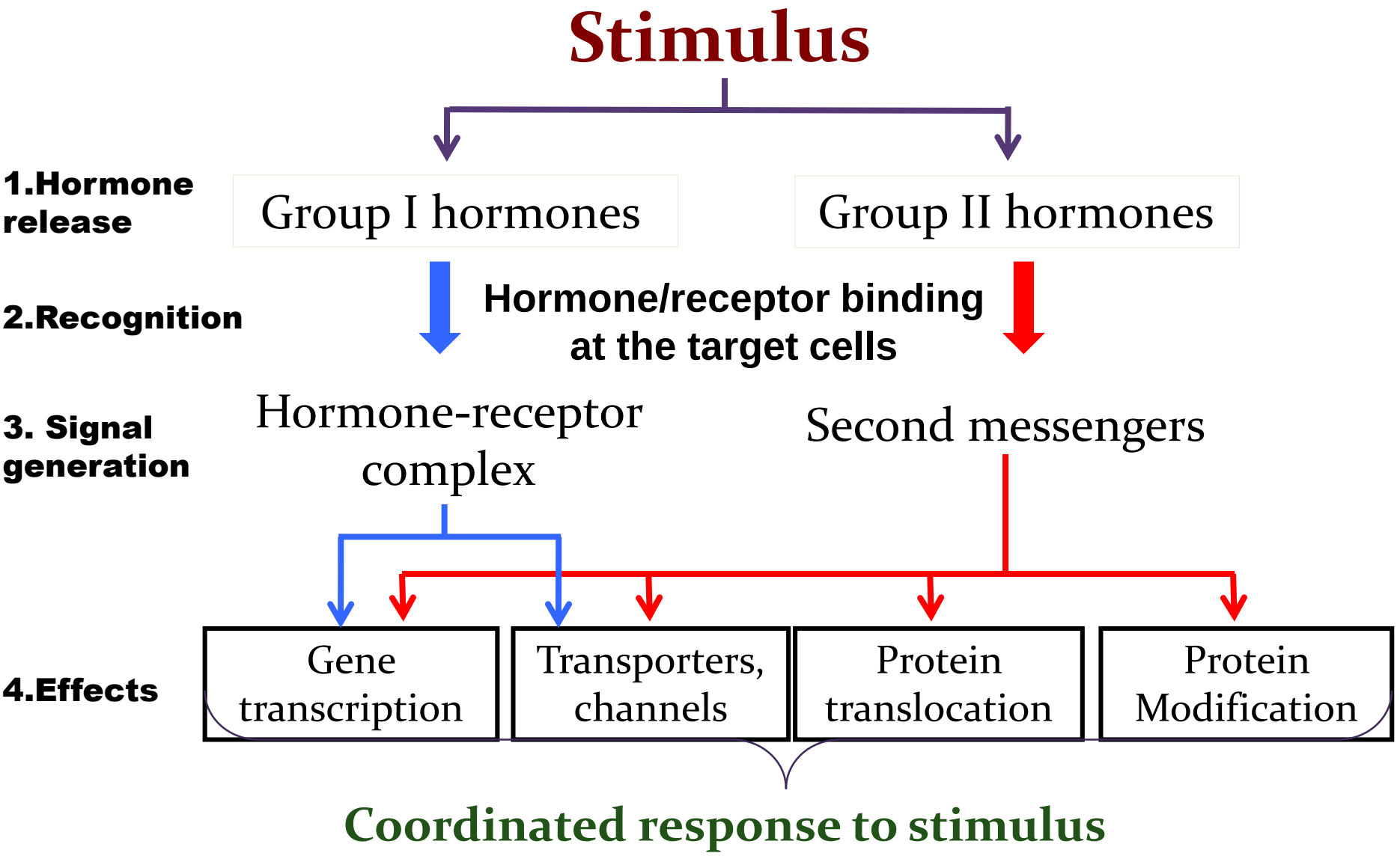
Background

- 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. 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**

CLASSIFICATION OF HORMONES



GENERAL FEATURES OF HORMONE CLASSES:

	Group I	Group II
Types	• Steroids • Thyroid Hs (T_3 & T_4) • Calcitriol • Retinoid	• Polypeptides • Glycoproteins • Catecholamine
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 • Metabolites of complex phosphpinositols • Tyrosine kinase cascades

***Lipophilic hormones need proteins to bind to in the Hydrophilic environment of plasma>>this will decrease their clearance>>increase their half life + since they're Lipophilic>> they can cross the cell membrane>>their Receptors will be waiting for them inside.**

CLASSIFICATION OF HORMONES BY MECHANISM OF ACTION

- A) Hormones that bind to intracellular receptors (Steroid-Thyroid superfamily)
- B) Hormones that bind to cell surface receptors*
  - 1) The 2nd messenger is cAMP
  - 2) The 2nd messenger is cGMP
  - 3) The 2nd messenger is calcium or phosphatidylinositol or both
  - 4) The 2nd messenger is a tyrosine kinase cascade

***Hydrophilic hormones are unable to pass through the phospholipid bilayer of the plasma membrane and are therefore dependent upon receptor molecules on the surface of cells 'need of 2nd messenger'.**

A) MECHANISM OF ACTION OF: STEROID -THYROID HORMONES

Steroid Hormones:

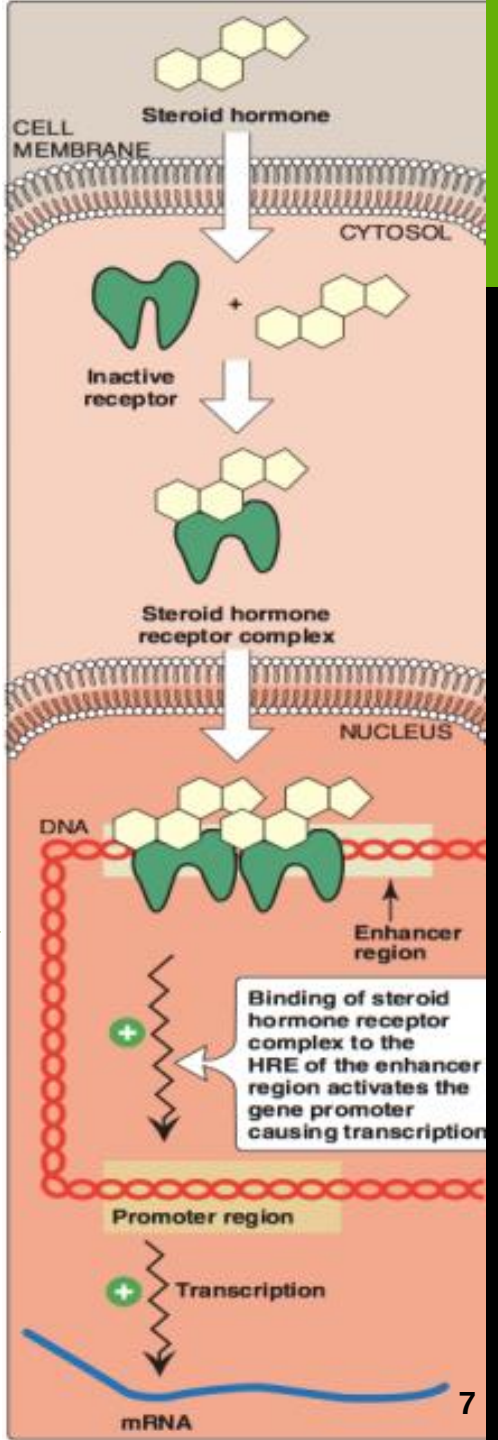
- Glucocorticoids
- Mineralocorticoids
- Sex hormones:
  - Male sex hormones : Androgens
  - Females sex hormones: Estrogens & Progestin

Thyroid Hormones (T_3 &T_4)

Calcitriol (1,25 $[OH]_2$ –D3) (Active form of vitamin D)

Retinoic acid

A Lipophilic Hormone will enter the cell>>bind to its receptor which is either in the *cytosol* "steroid hormones" or in the *nucleus* "thyroid hormones" to form hormone-receptor complex>> hormone-receptor complex will bind to HRE* of the enhancer region>>gene transcription



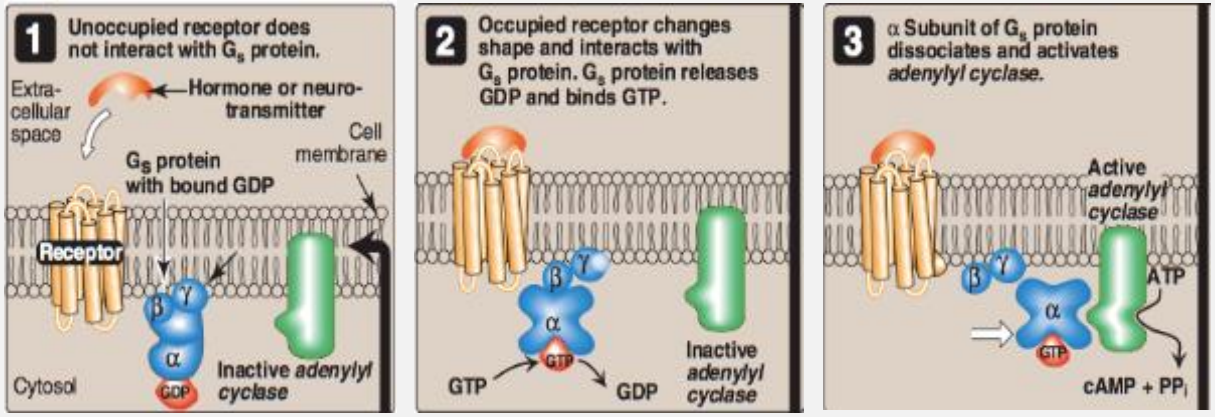
*HRE: A hormone response element (HRE) is a short sequence of DNA within the promoter of a gene that is able to bind a specific hormone-receptor complex and therefore regulate transcription.

B) HORMONES THAT BIND TO CELL SURFACE RECEPTORS

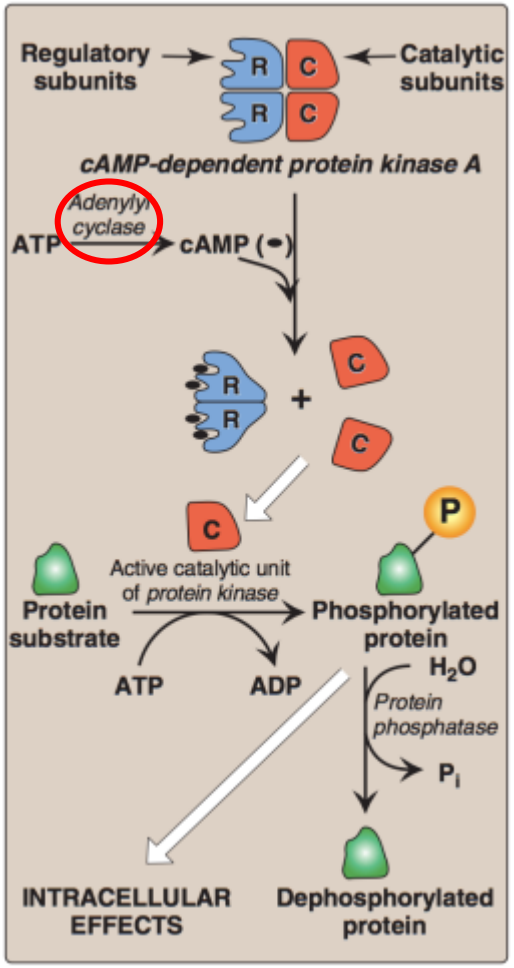
1) The second messenger is cAMP

- Catecholamines (α2- Adrenergic)
- Catecholamines (β- Adrenergic)
- Ant.Pituitary: ACTH, FSH, LH & TSH
- ADH (Renal V_2 –receptor)
- Calcitonin & PTH
- Glucagon

Cascade for formation of cAMP by cell-surface hormones



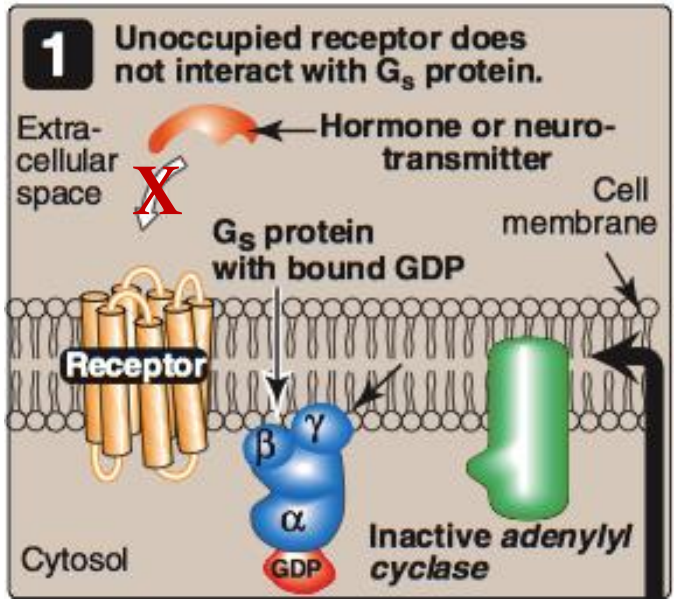
Actions of cAMP

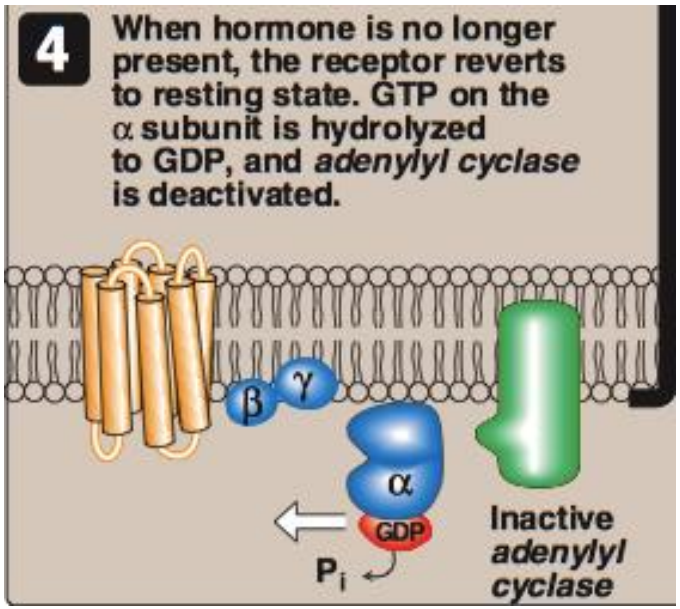


ACTH = adrenocorticotropic hormone. TSH = Thyroid-stimulating hormone. PTH = Parathyroid hormone

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





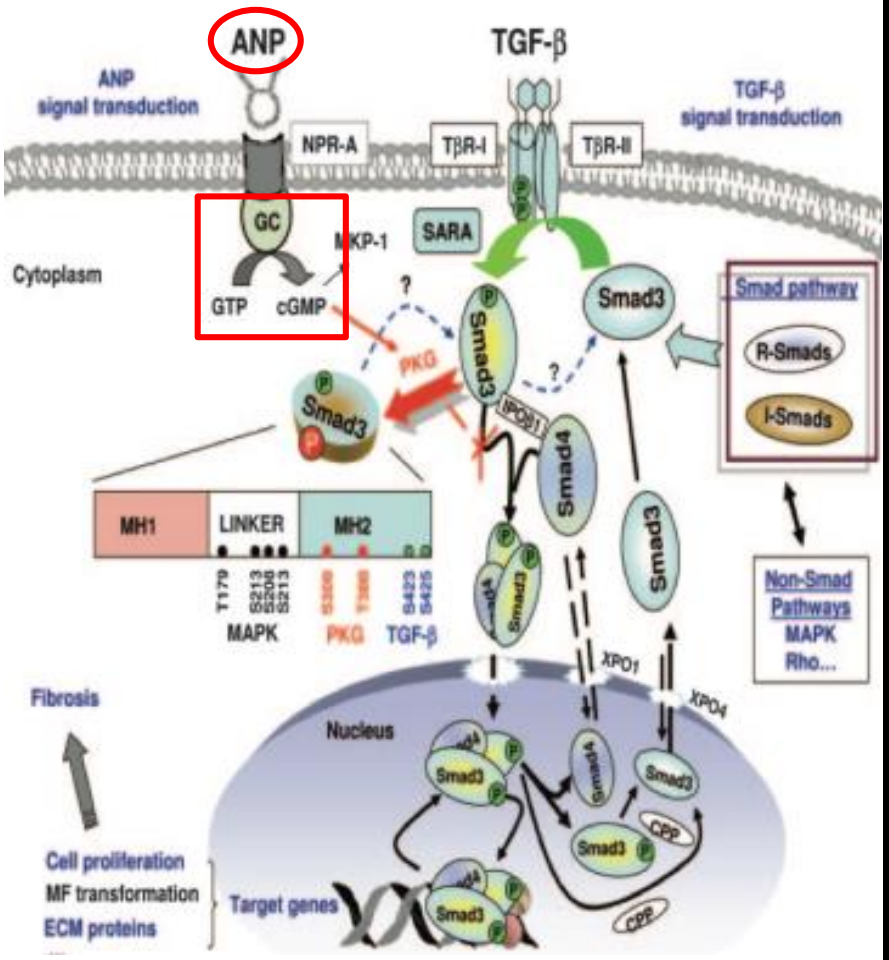
Important slide(Especially the enzymes)

B) HORMONES THAT BIND TO CELL SURFACE RECEPTORS

2) The second messenger is cGMP

- Atrial Natriuretic Peptide (ANP)
- Nitric Oxide

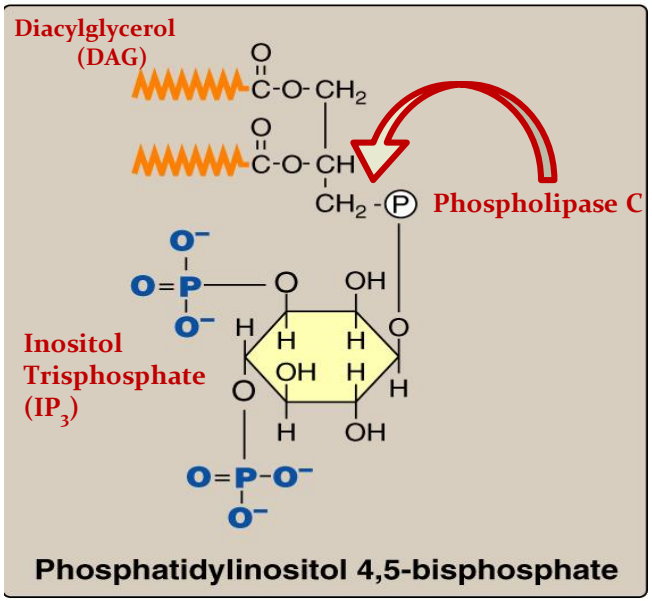
- **Guanaylate cyclase (GC)** converts GTP to cGMP (2nd messenger)
- ANP = Powerful vasodilator It is involved in:homeostatic control of body water, sodium, potassium.

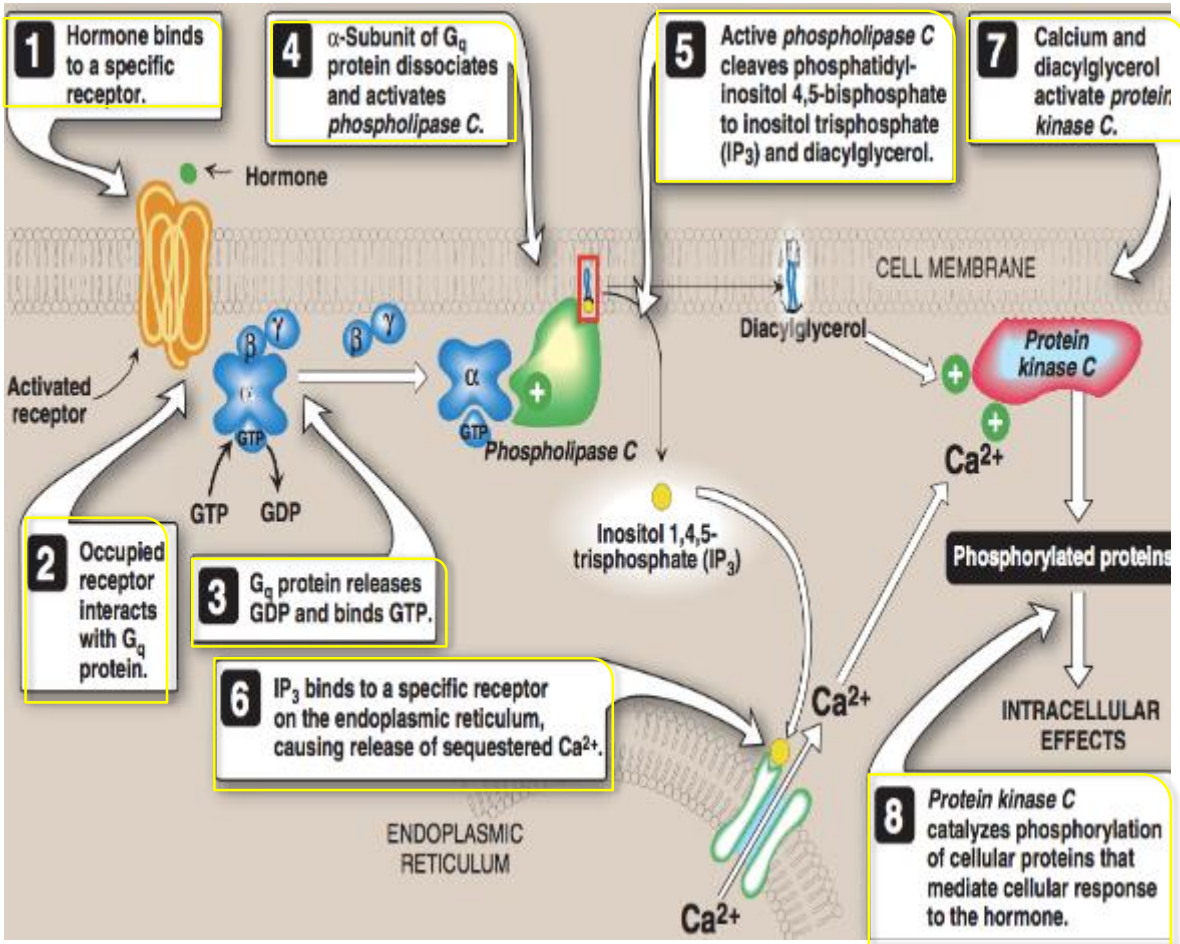


B) HORMONES THAT BIND TO CELL SURFACE RECEPTORS

3) The 2nd messenger is calcium or phosphatidylinositol or both

- Acetylcholine (muscarinic)
- Catecholamines (α1- Adrenergic)
- Angiotensin II
- ADH[1] (vasopressin): Extra-renal V_1 receptor





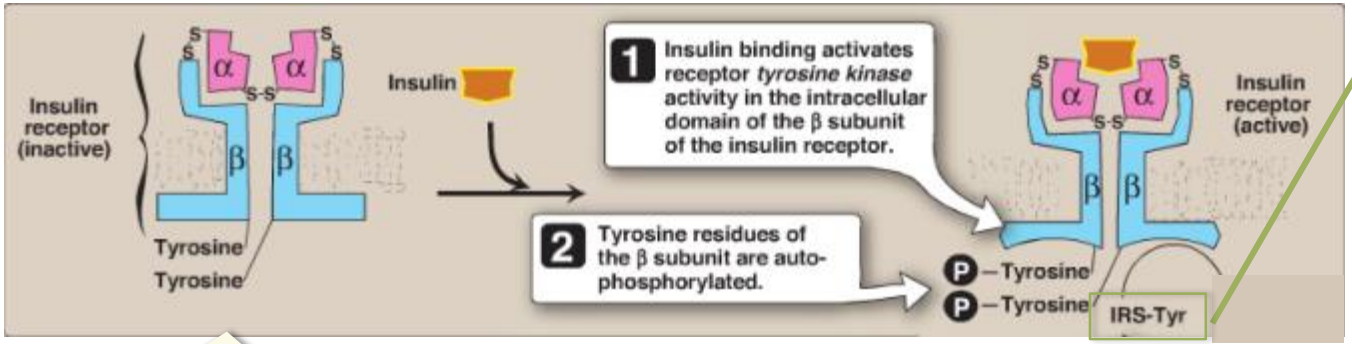
1. ADH = water retention (increase water and sodium reabsorption in kidney)

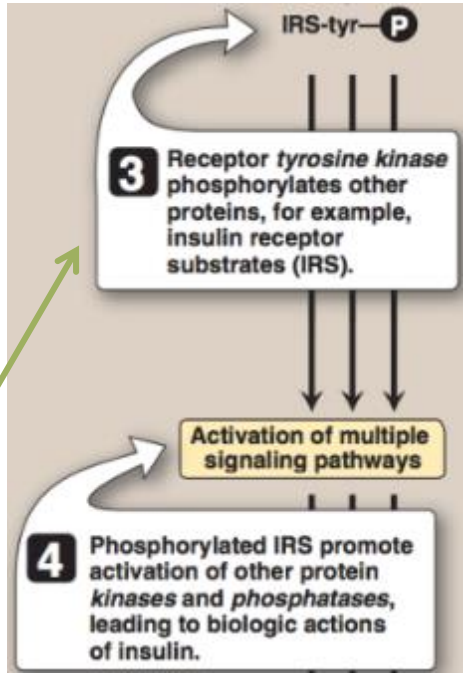
B) HORMONES THAT BIND TO CELL SURFACE RECEPTORS

4)The second messenger is a tyrosine kinase cascade

- GH & Prolactin
- Insulin
- Erythropoietin

MECHANISM OF INSULIN ACTION:





❖ EXTRA:

-Alpha subunit: responsible for recognizing and binding to insulin. binding of insulin to the α subunits of the insulin receptor
induces conformational changes that are transmitted to the β subunits.

Beta subunit: contains a hydrophobic domain which spans the plasma membrane + intracellular domain (contains the tyrosine residue that will be phosphorylated after binding to the insulin)

✓ So the Receptor its self is phosphorylated (autophosphorylation).This Autophosphorylation initiates a cascade of cell-signaling responses, including phosphorylation of a family of proteins called insulin receptor substrates (IRSs).

Biologic Effects of Insulin

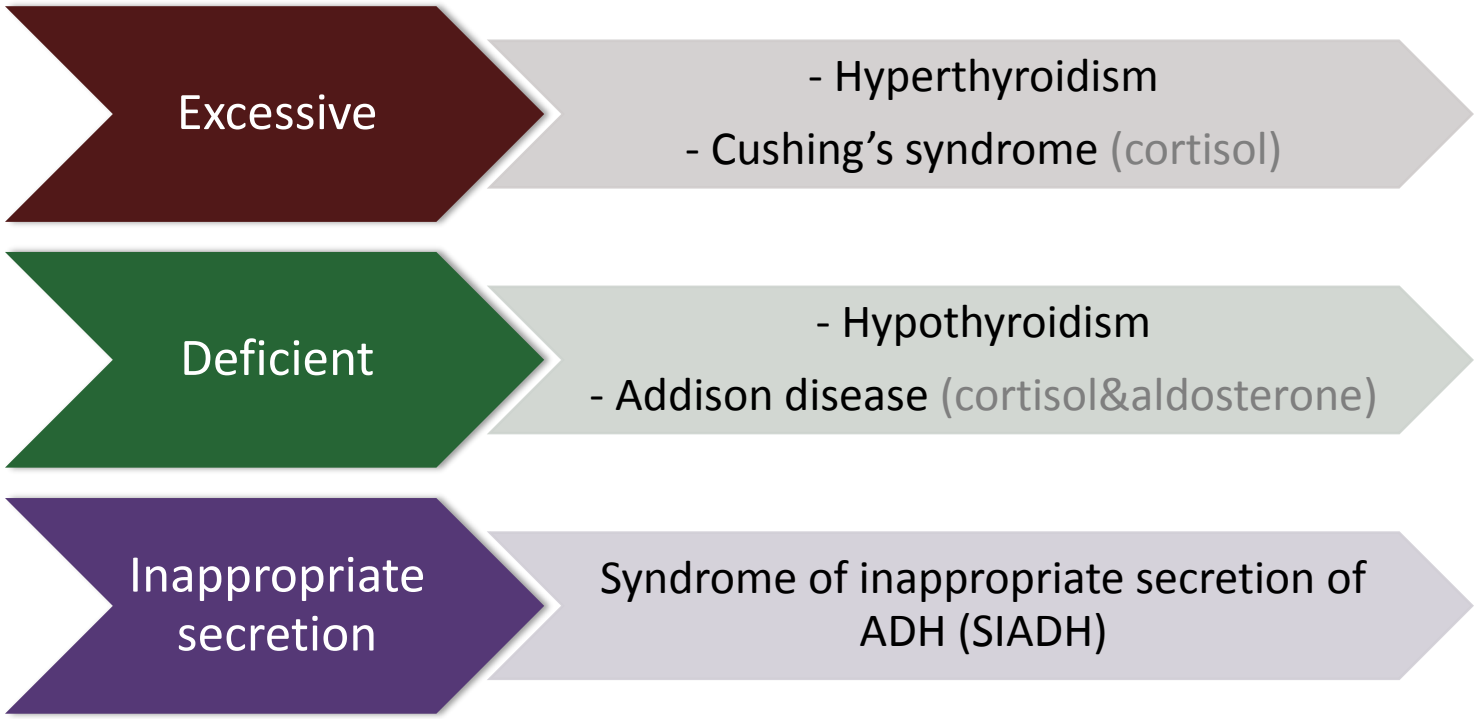
Increase

-Glucose uptake -Glycogen synthesis -Protein synthesis -Fat synthesis	-Gluconeogenesis -Glycogenolysis -Lipolysis

Decrease

Altered gene expression

BIOMEDICAL IMPORTANCE OF HORMONES



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

SUMMARY

	Group 1	Group 2			
Receptor	**Intracellular**	**Bind to the surface**			
2nd messenger	Receptor intracellular	cAMB	cGMP	Ca + & phosphatidylinositol	Tyrosine kinase
Examples	1. Steroids (sex hormones) 2. Thyroid hormones T3 , T4 3. Calcitriol 4. Retinoic acid	1. 1.Catecholamines (α_2- Adrenergic) 2. 2.Catecholamines (β- Adrenergic) 3. 3. Ant. Pituitary: ACTH, FSH, LH & TSH 4. 4. ADH (Renal V2-receptor) 5. 5. Calcitonin & PTH 6. 6. Glucagon	1. Atrial natriuretic peptide (ANP) 2. Nitric oxide	1. Acetylcholine (muscarinic) 2. Catecholamines (α_1- Adrenergic) 3. Angiotensin II 4. ADH (vasopressin): Extra-renal V1 receptor	1. GH & Prolactin 2. Insulin 3. Erythropoietin

MCQS

1. The action of inositol triphosphate (IP3) is?

A. to activate protein kinase C
B. to activate adenylyl cyclase
C. to release Calcium from endoplasmic retiulum
D. to activate protein kinase A

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

A. CA/phosphatidylininositol (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 lypolysis
C. Increase glycogenolysis
D. Decrease glucose uptake

4. In CA/phosphatidylininositol 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

6. Which one of the following is hydrophilic :

A. Glucocorticoids
B. Progestin
C. Epinephrine
D. Retinoic acid

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

A. Adenylyl cyclase
B. Phospholipase
C. Protein kinase A
D. Guanaylate cyclase

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

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

9. The second messenger for atrial natriuretic peptide is :

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

10. Which one of the following hormones does NOT need second messenger to do its action :

A. FSH
B. Estrogen
C. LH
D. Insulin

1-C 2-A 3-A 4-B 5- B 6-C 7-D 8-A 9-B 10- B

SAQS

What's factors determine the response of 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

What are the mechanism of action of a hormone to produce an effect?

1. group 1 hormones : gene transcription , transporters channels
2. group 2 hormones : gene transcription , transporters, channels , protein translocation , protein modification

How to stop hormonal stimulus of cAMP :

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 $\beta\gamma$-subunits
7. Inactivation of adenylyl cyclase

Biochemistry Bandits 434

اللهم إني استودعتك ما قرأت وما حفظت وما تعلمت فرده لي
عند حاجتي إنك على كل شيء قدير

DONE BY:

Mada AlBatli

Aya AlDayel

REVISED BY:

Ameera Zuair

Najla Aldraiweesh