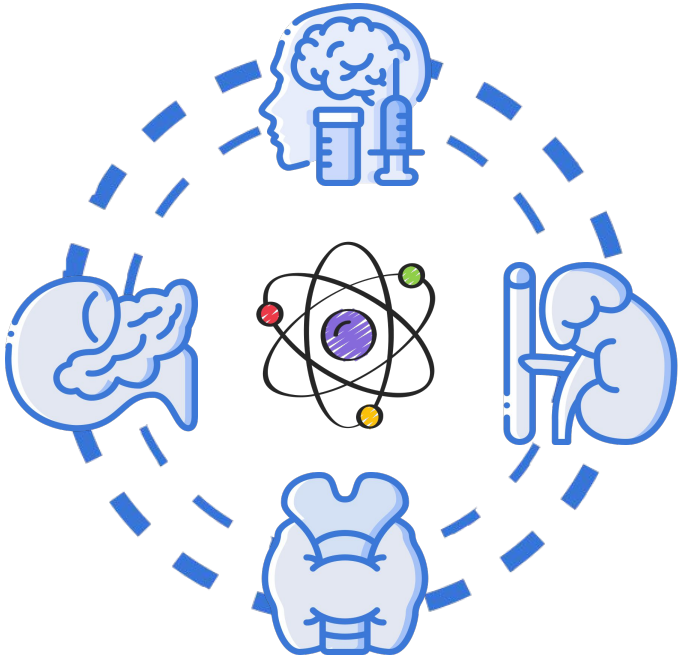
General Mechanisms of Hormone Actions



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- Main Topic
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- Extra info

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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.

Outlines:

- 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 and 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:

01

The **rate of synthesis & secretion** of the hormones

02

The **conversion** of **inactive** forms of the hormone into the **fully active** form

03

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

04

The number, relative activity, and state of **occupancy** of the **specific receptors**

05

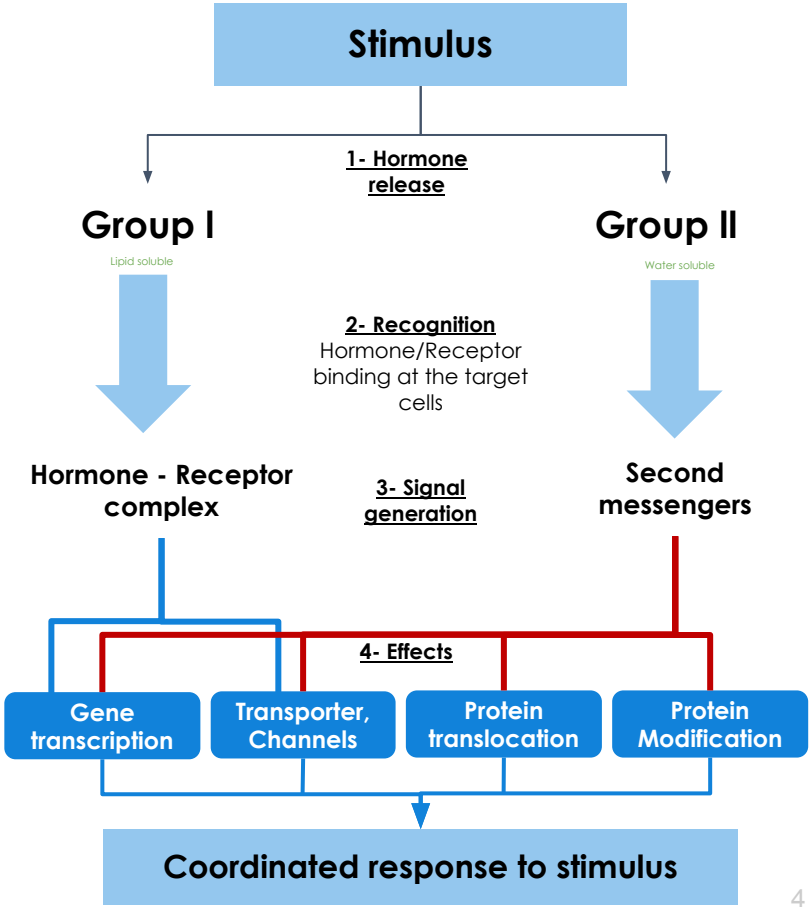
Post-receptor factors

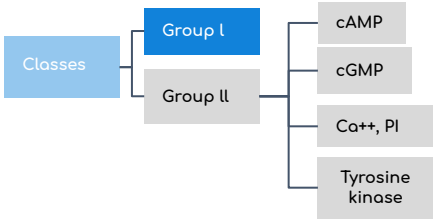
E.g. Central dogma if the goal of the hormone was protein synthesis.

Classification of Hormones

The table is very important

	Group I (Steroid-Thyroid superfamily)	Group II
Types	• Steroid • Thyroid Hs(T4,T3) • Calcitriol (Active form of Vitamin D, 1,25$(OH)_2$-D_3) • Retinoids (Retinoic acid)	• 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++, Metabolites of complex phosphoinositols, Tyrosine kinase cascade.

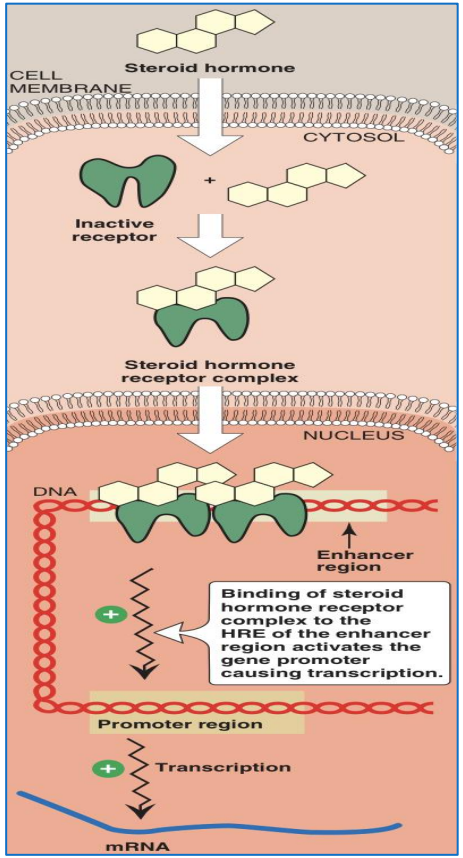




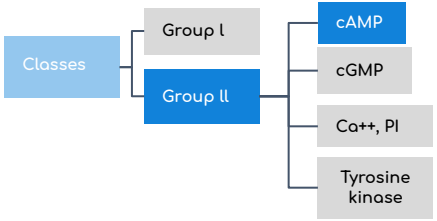
Classification of Hormones Based on Mechanism of Action

1 Hormones that bind to intracellular receptors (Steroid-Thyroid superfamily):

- **Steroid Hormones:**
  - Glucocorticoids
  - Mineralocorticoids
  - Sex hormones:
    - Male sex hormones: **Androgens**
    - Female sex hormones: **Estrogens & Progestins**
- **Thyroid Hormones (T3 & T4)**
- **Calcitriol (1,25[OH]2-D3)**
- **Retinoic acid**



Explanation for the PIC:
Each **steroid hormone diffuses across the plasma membrane** of its target cell and **binds to a specific cytosolic or nuclear receptor.** These receptor–ligand complexes accumulate in the nucleus, dimerize, and bind to specific regulatory DNA sequences (hormone response elements, HRE) in association with coactivator proteins, thereby causing promoter activation and **increased transcription of targeted genes.** An HRE is found in the promoter or enhancer element for genes that respond to a specific steroid hormone, thus ensuring coordinated regulation of these genes. Hormone–receptor complexes can also inhibit transcription in association with corepressors.



Classification of Hormones Based on Mechanism of Action cont.

2 Hormones that bind to cell surface receptors.

A- Second messenger: cAMP

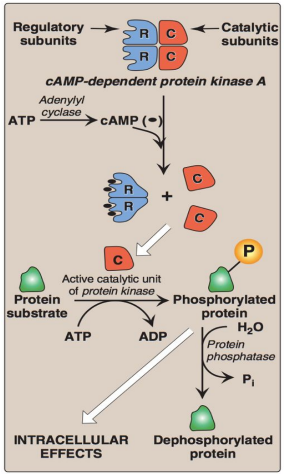
Examples are important Memorize each hormone and its mediators

- Catecholamines (α2- Adrenergic)
- Catecholamines (beta- Adrenergic)
- Ant. Pituitary: ACTH, FSH, LH & TSH
- ADH (Renal V2-receptor)
- Calcitonin & PTH
- Glucagon

2- Actions of cAMP:

Explanation for the PIC:

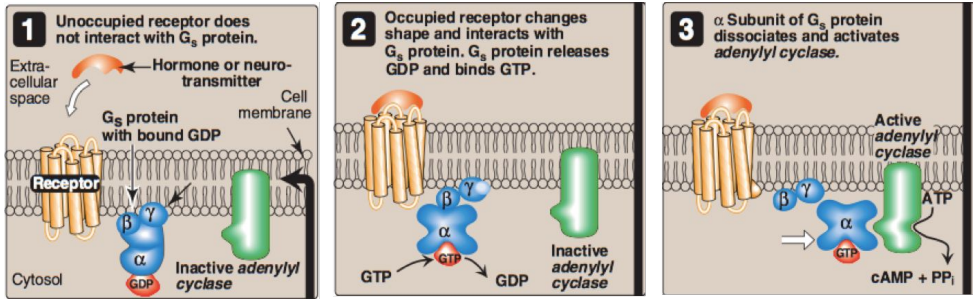
Cyclic AMP activates protein kinase A by binding to its two regulatory subunits, causing the release of active catalytic subunits. The active subunits catalyze the transfer of phosphate from ATP to specific serine or threonine residues of protein substrates. The phosphorylated proteins may act directly on the cell's ion channels, or, if enzymes, may become activated or inhibited. Protein kinase A can also phosphorylate proteins that bind to DNA, causing changes in gene expression. The phosphate groups added to proteins by protein kinases are removed by protein phosphatases. This ensures that changes in protein activity induced by phosphorylation are not permanent.

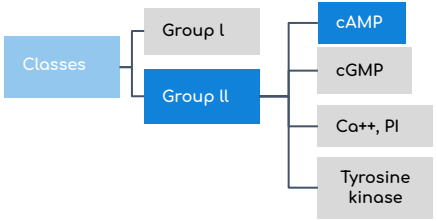


1- Cascade for formation of cAMP by cell-surface hormones:

Explanation for the PIC:

The effect of the activated, occupied GPCR on second messenger formation is not direct but, rather, is mediated by specialized trimeric proteins (α, β, γ subunits) of the cell membrane. These proteins, referred to as G proteins because they bind guanosine nucleotides (GTP and GDP), form a link in the chain of communication between the receptor and adenylyl cyclase . **In the inactive form of a G protein, the α-subunit is bound to GDP, Binding of ligand causes a conformational change in the receptor, triggering replacement of this GDP with GTP. The GTP-bound form of the α subunit dissociates from the βγ subunits and moves to adenylyl cyclase, which is thereby activated and convert ATP into cAMP.** Many molecules of active Gα protein are formed by one activated receptor.





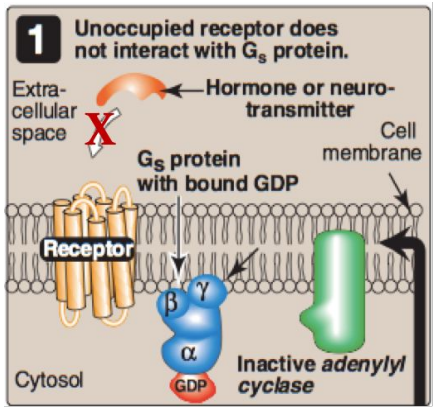
Classification of Hormones Based on Mechanism of Action cont.

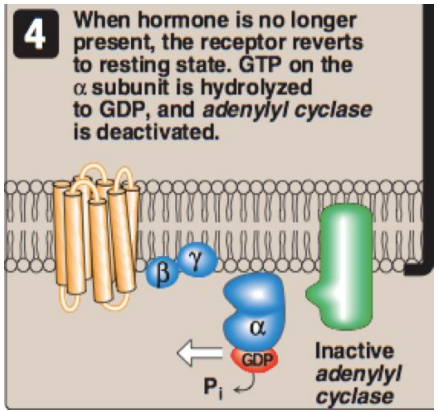
2 Hormones that bind to cell surface receptors.

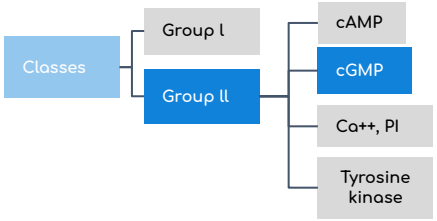
A- Second messenger: cAMP

3- 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 a-subunit to βγ-subunits
7. Inactivation of adenylyl cyclase







Classification of Hormones Based on Mechanism of Action cont.

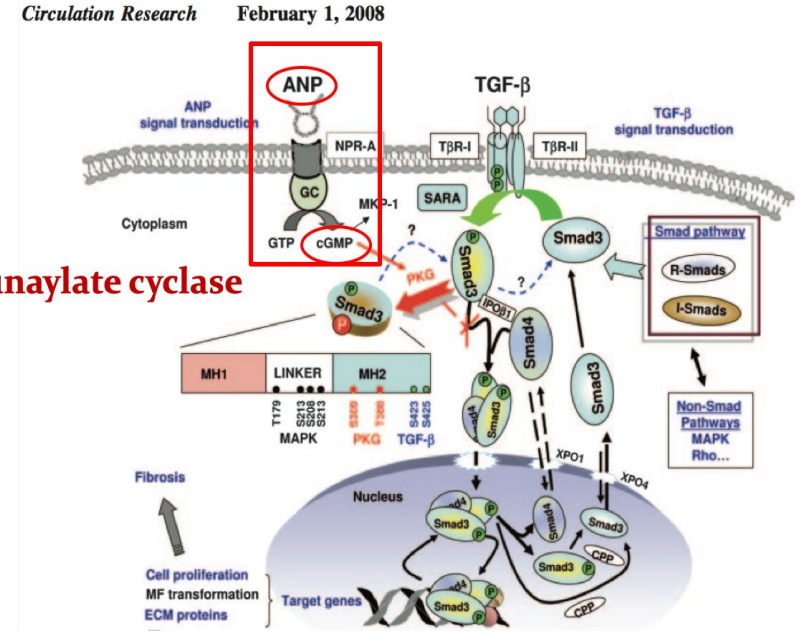
2 Hormones that bind to cell surface receptors.

B- Second messenger: cGMP

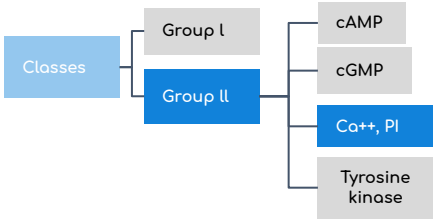
- Atrial natriuretic peptide (ANP)
- Nitric oxide

Doctor said you only need to know what's in red, the downstream reactions aren't important.

Explanation for the PIC:
ANP binds to NPR-A(natriuretic peptide receptor-A) which will activate Guanylate cyclase protein leading to the conversion of GTP into cGMP. cGMP will activate PKG (Protein kinase G) which will phosphorylate Smad3 inhibiting it from upregulating collagen synthesis.
NOTE: Normally when TGF-beta binds to the cell surface receptor it will phosphorylate SMAD3(Has 1 phosphate), then SMAD3 will bind to SMAD4, upregulating the synthesis of Extracellular matrix proteins and myofibroblast transformation leading to fibrosis.



GC: Gunaylate cyclase



Classification of Hormones Based on Mechanism of Action cont.

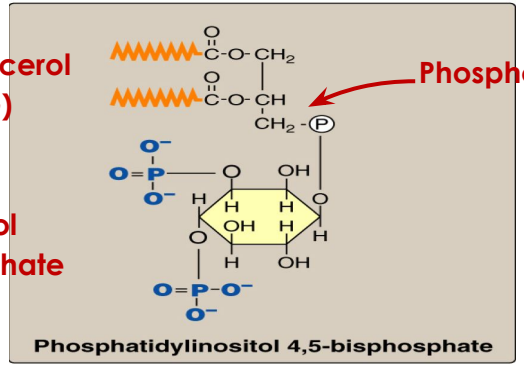
2 Hormones that bind to cell surface receptors.

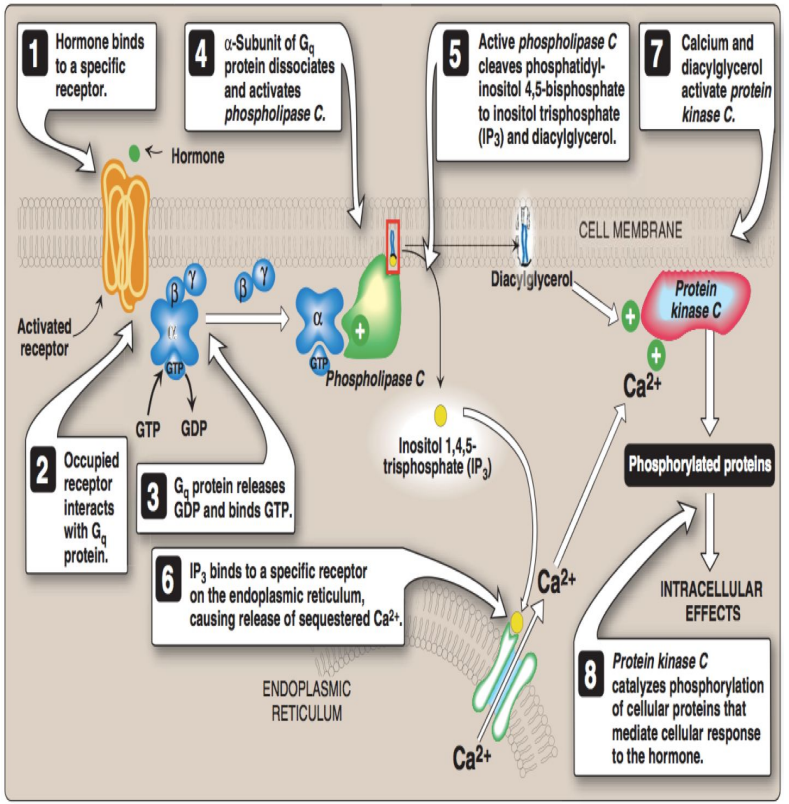
C- Second messenger: calcium or phosphatidylinositol (or both)

- Acetylcholine (muscarinic)
- Catecholamines (α1- Adrenergic)
- Angiotensin II
- ADH (vasopressin): Extra-renal V1-receptor

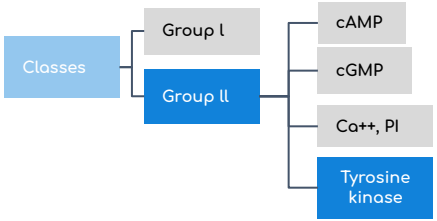
Calcium / Phosphatidylinositol System:

PIP2 is cleaved by Phospholipase C into DAG and IP3





Don't skip it, it's important :)



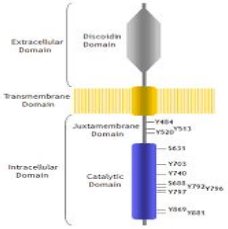
Classification of Hormones Based on Mechanism of Action cont.

The figure is important

2 Hormones that bind to cell surface receptors.

D- Second messenger: Tyrosine kinase cascade

- **Insulin**
- **GH & Prolactin**
- **Erythropoietin**



Mechanism of insulin action:

Explanation for the PIC:

- The insulin receptor is synthesized as a single polypeptide that is glycosylated and cleaved into a and β subunits, which are then assembled into a tetramer linked by disulfide bonds.
- The **binding of insulin to the a subunits of the insulin receptor induces conformational changes that are transduced to the β subunits. This promotes a rapid auto phosphorylation of specific tyrosine residues on each β subunit. Autophosphorylation initiates a cascade of cell signaling responses, including phosphorylation of a family of proteins called insulin receptor substrates (IRS)**. Phosphorylated IRS proteins interact with other signaling molecules through specific domains, activating a number of pathways that affect gene expression, cell metabolism and growth. The actions of insulin are terminated by dephosphorylation of the receptor.

★ **What are the biologic effects of insulin? (Check the figure)**

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)**

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

	Group I (Steroid-Thyroid superfamily)	Group II
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma half-life	Long (Hours-Days)	Short (Minutes)
Receptor	Intracellular	Plasma membrane

Classes

Group I

- **Steroid Hormones:**
  - Glucocorticoids
  - Mineralocorticoids
  - Sex hormones:
    - **Male sex hormones:** Androgens
    - **Female sex hormones:** Estrogens & Progestins
- **Thyroid Hormones (T3 & T4)**
- **Calcitriol (1,25[OH]2-D3)**
- **Retinoic acid**

Group II

cAMP

- **Catecholamines (a2-Adrenergic)**
- **Catecholamines (beta-Adrenergic)**
- **Ant. Pituitary: ACTH, FSH, LH & TSH**
- **ADH (Renal V2-receptor)**
- **Calcitonin & PTH**
- **Glucagon**

cGMP

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

Ca++&PI

- **Acetylcholine (muscarinic)**
- **Catecholamines (a1- Adrenergic)**
- **Angiotensin II**
- **ADH (vasopressin): Extra-renal V1-receptor**

Tyrosine kinase

- **Insulin**
- **GH & Prolactin**
- **Erythropoietin**

Quiz

MCQs :

Q1: Which of the following uses cGMP as a second messenger?
a) Insulin **b)** Glucagon **c)** Adrenaline **d)** ANP

Q2: When Angiotensin II binds to its receptor it will lead to the activation of?
a) Adenylate cyclase **b)** Phospholipase C
c) Guanylate cyclase **d)** Hydroxylase

Q3: Which of the following doesn't require a second messenger for its action?
a) ANP **b)** AcH **c)** Estrogen **d)** Erythropoietin

Q4: Which of the following systems mediates the action of insulin?
a) cAMP **b)** cGMP **c)** Tyrosine kinase **d)** Ca++,PIP2

Q5: Which of the following substance uses Ca++,DAG&IP3 as its 2nd messenger?
a) Catecholamines (a2- Adrenergic) **b)** Catecholamines (a1- Adrenergic)
c) Catecholamines (beta- Adrenergic) **d)** Retinoic acid

Q6: Which of the following is characteristic of low insulin levels?
a) Increased glycogen synthesis **b)** Decreased gluconeogenesis from lactate.
c) Decreased Glycogenolysis **d)** Increased formation of 3-hydroxybutyrate(Ketone body).

SAQs :

Q1: Mention 2 Hormones that utilize cGMP to produce their action.

Q2: Compare between thyroid hormones and glucagon in terms of: Solubility, transport proteins, plasma half-life and receptor location.

Q3: Mention 3 biological effects of insulin.

★ **MCQs Answer key:**

1) D 2 B 3) C 4) C 5)B 6) D

★ **SAQs Answer key:**

1) ANP, NO

2) Apply the table in slide 4

3) 1- Increase glycogen synthesis, 2- Increase fat synthesis , 3- increase protein synthesis.

Team members

Girls Team:

- Ajeed Al-Rashoud
- Alwateen Albalawi
- Amira AlDakhilallah
- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
- Nouf Alhumaidhi
- Noura Alturki
- Sarah Alkhalife
- Shahd Alsalamah
- Taif Alotaibi

Boys Team:

- Alkassem Binobaid
- Fares Aldokhayel
- Khayyal Alderaan
- **Mashal Abaalkhail**
- Naif Alsolais
- Omar Alyabis
- Omar Saeed
- Rayyan Almousa
- Yazen Bajeaifer

Team Leaders

Lina Alosaimi

Mohannad Alqarni

★ We can either walk towards Growth, or stand in Safety

438 BIOCHEMISTRY TEAM

We hear you