General Mechanisms of Hormone Actions

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**

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)

General Mechanism Of Hormones

1- Stimulus		
2- Hormone release	Group I hormones	Group II hormones
3- Recognition	Hormone/receptor binding at the target cells	
4- Signal generation	Hormone-receptor complex	Second messengers
5- Effects	Gene transcription Transporters, channels	Protein Modification Protein translocation Gene transcription Transporters, channels
	Coordinated response to stimulus	

General Features of Hormone Classes

	Group I hormones	Group II hormones
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

Classification of Hormones by Mechanism of Action

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

1- **Steroid Hormones:**
   - Glucocorticoids
   - Mineralocorticoids
   - Sex hormones:
     - Male sex hormones: Androgens
     - Female sex hormones:Estrogens & Progestins
2- **Thyroid Hormones (T_3 & T_4)**
3- **Calcitriol ($1,25[OH]_2$-D_3)** (active form of vitamin D, $1,25[OH]_2$-D_3)
4- **Retinoic acid**

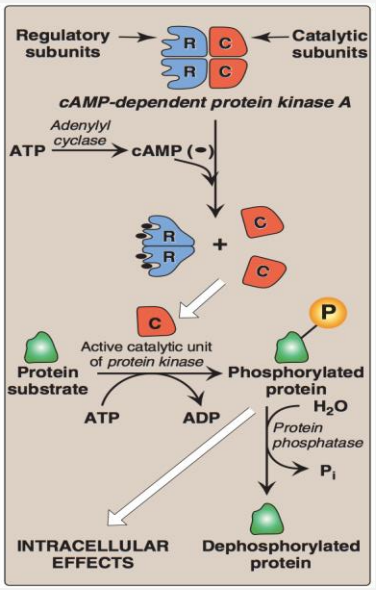
Mechanism of Action of Steroid-Thyroid Hormones :

1- Steroid hormones **diffuse** across the plasma membrane of its target cell.
2- Binds to a specific "Cytosolic" or "Nuclear" receptor and forms "**Receptor ligand complex**".
3- That complex accumulates, dimerizes, and binds to **hormone response element (HRE)** "a specific regulatory DNA sequence" in association with either coactivator or corepressor.
4- This cause **promotor activation\inhibition** and increased\decreased transcription of the targeted gene depending on the hormone.

II. Hormones that bind to cell surface receptors

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
• **Catecholamines (α_2- Adrenergic)** • **Catecholamines (β- Adrenergic)** • **Ant. Pituitary: ACTH, FSH, LH & TSH** • **ADH (Renal V2-receptor)** • **Calcitonin & PTH** • **Glucagon**	• **Atrial natriuretic peptide (ANP).** • **Nitric oxide (NO).**	• **Acetylcholine (muscarinic)** • **Catecholamines (α1-Adrenergic)** • **Angiotensin II** • **ADH (vasopressin): Extra-renal V1-receptor**	• **GH & Prolactin** • **Insulin** • **Erythropoietin**
Mechanism :	**Mechanism:**	**Mechanism**	**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.	1. **Direct** activation of **Gunaylate cyclase**. 2. Activated GC converts GTP to cGMP.	1- Hormone binds to **G-protein coupled receptor.** 2- Receptor Interacts with G-protein Which releases **GDP and binds with GTP.** 3. α subunit dissociates from βγ-subunits, and activates **Phospholipase C.**	Insulin receptor is a **dimer** that consists of 2 identical units. Each unit has: A- **An alpha-chains**: on the **outside** and create a binding site for **insulin**. B- **A beta-chains:** Spans the plasma membrane and its cytosolic domain is a **tyrosine kinase**.

Actions of cAMP



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 **phosphodiesteras**
4- Inactivation of protein kinase A by a decrease of cAMP
5- Hydrolysis of GTP into GDP
6- Binding of α-subunit to βγ-subunit
7- Inactivation of adenylyl cyclase .

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.

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

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.

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