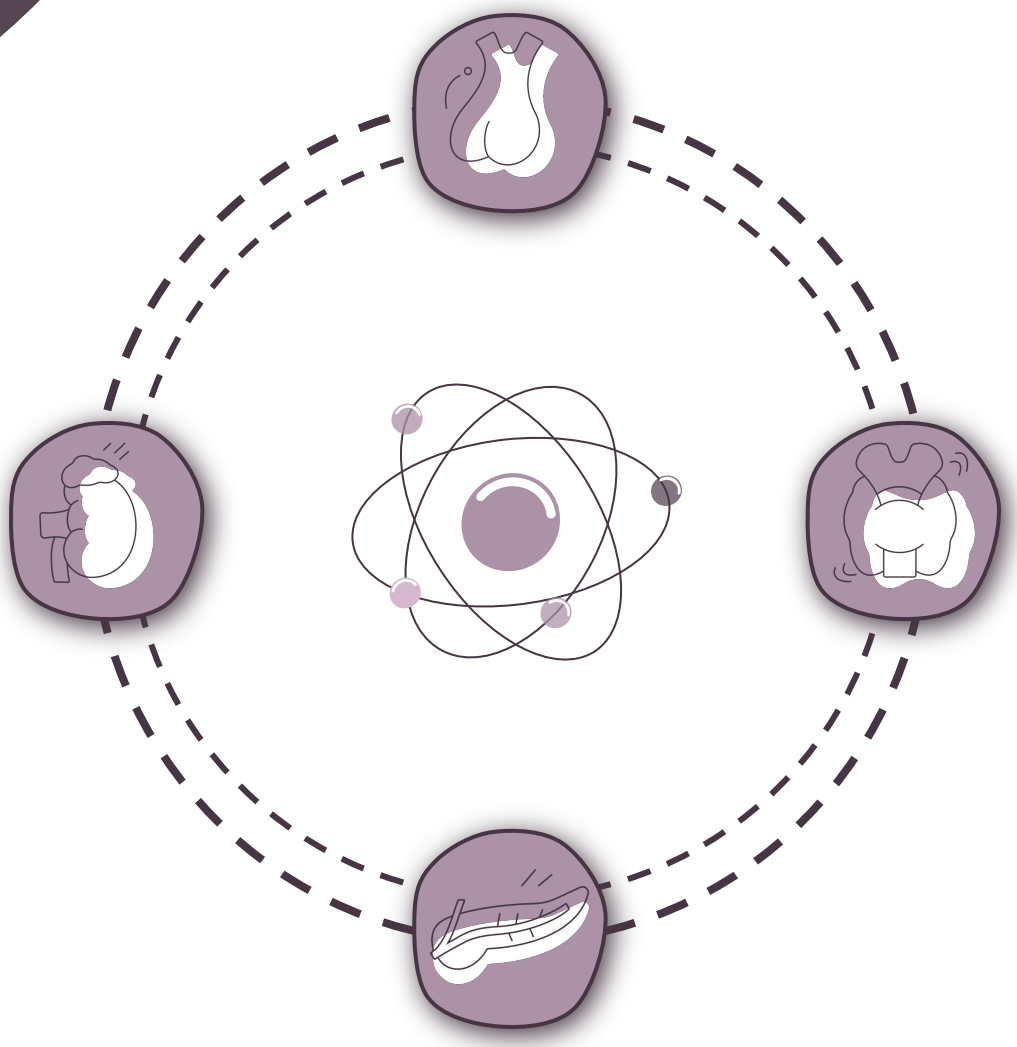
Biochemistry
Team 443



L2: General mechanism of actions of hormones

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Color Index:
Main Text
Male's Slides
Female's Slides
Important
Doctor's Notes
Extra Info

Editing File link:

Objectives

1. Acquire the **knowledge** for general consequence of hormone-receptor interaction
2. Understand different **mechanisms of action** of hormones
3. Recognize the **biomedical importance** due to disturbance in the normal mechanisms of hormonal action

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1

Background

- Multicellular organisms depend in their survival on their adaptation to a constantly changing environment
- Intercellular (between the cells) communication is necessary for this adaptation to take place (to tell other cells about the changes)
- 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 e.x. growth hormone tells the muscle cells to synthesize certain proteins and liver cells to synthesis IGF-1. This is plurality in its action.
- A target is any cell in which the hormone (ligand: the binding part of the hormone) binds to its receptor The cells that are going to give you a biological response to a hormone. What makes the cell a target is that it has receptors to recognize that hormone.
  If clearance is impaired, the hormone will remain bound to the target cell, and the newly secreted hormone will not find a binding site.

Factors Determining The Response Of A Target Cell To A Hormone

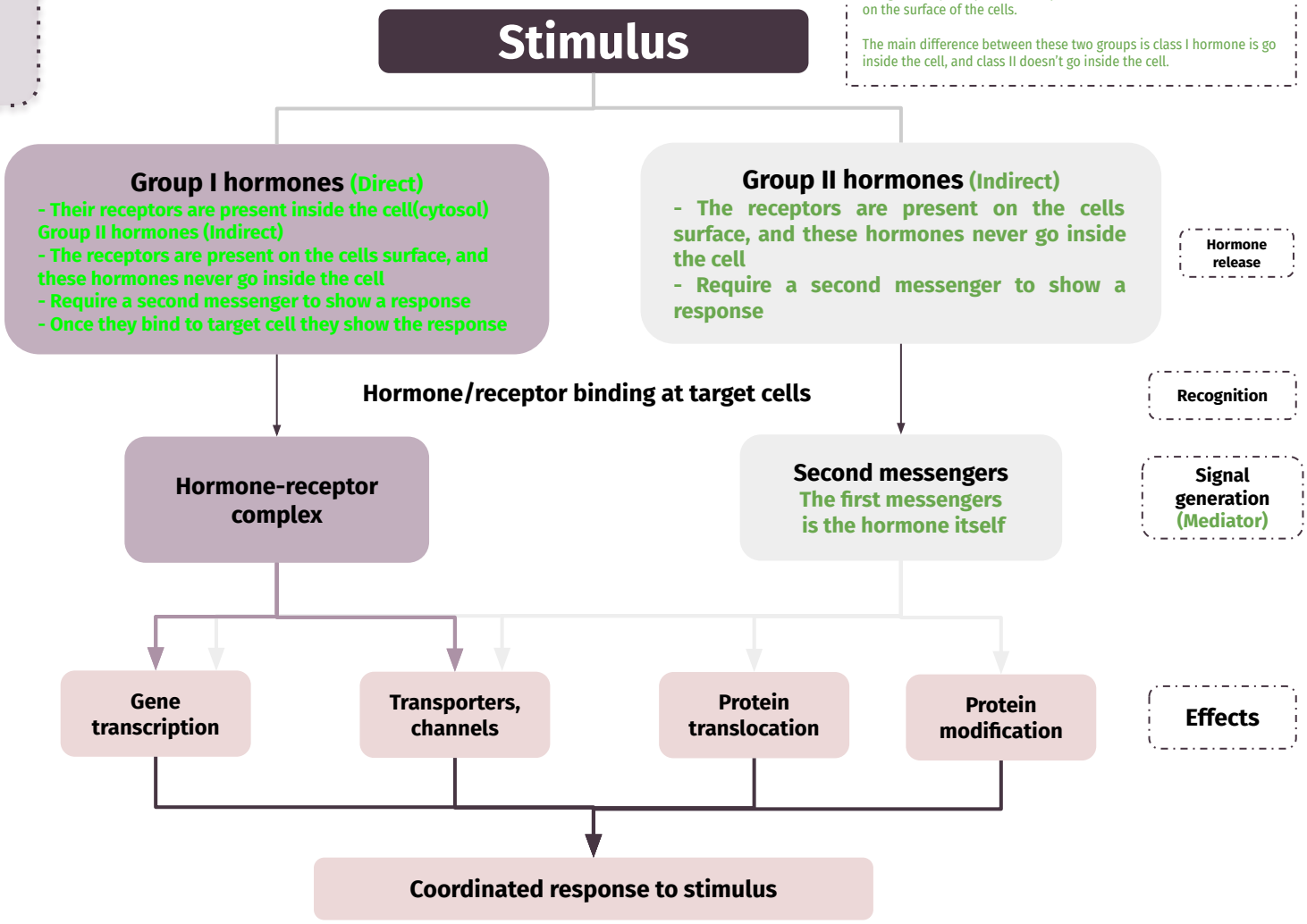
1. **The rate of synthesis & secretion of the hormones.** Sometimes the hormone is synthesized before the stimulus and secreted after the stimulus. Sometimes the stimulus leads to synthesis of hormone.
2. **The conversion of inactive forms of the hormone into the fully active form** Most hormones are secreted in their active form, but a few are secreted in their inactive form.
3. **The rate of hormone clearance from plasma (half-life & excretion).** (How long is it going to stay in plasma) If the hormone is cleared from plasma very soon, then the response will be seen in smaller degree, but If the hormone is a protein bound hormone and stays in plasma for a long time (longer half life), then you will have longer and bigger response.
4. **The number, relative activity, and state of occupancy of the specific receptors**
5. **Post-receptor factors**

Why do we need hormones? To regulate body function.
- hormones are very essential for any cell's survival, if there is changes happening around it, then it should be able to adapt it (If it is multicellular or unicellular it doesn't matter).
- If the cell not able to adapt itself, it will lead to cell death or deleterious effect on the body.
- there is something that happening in the microenvironment of the different tissues, If the blood has high level of glucose, and the cells are not able to clear that glucose from bloodstream it's going to cause hyperglycemia. Or if the glucose level is too low then it will cause hypoglycemia, then it will cause effects may lead to coma and death.
- there is different way for communication: channels and electrical impulses. One of the ways which is usually for cells which are distance, so a cell picking up that stimulus of any change happen in the body, and tells the cells which are far from it, so it needs to synthesis a some molecule that can travel and tell the other cells, Those cells we call them the target cells (will give you the response)

2

Stimulus→ hormone release→ recog... by receptors→ the recognition by receptors can be presen inside the cell (intracellular) or on the surface of the cells.

The main difference between these two groups is class I hormone is go inside the cell, and class II doesn't go inside the cell.



General Features Of Hormone Classes

	Group 1 Called steroid thyroid superfamily	Group 2
Types	**Steroids** (glucocorticoid and mineralocorticoid) **Thyroid Hs (T3 & T4)** two vitamins which are acting as hormones: **Calcitriol** vitamin D **Retinoids** vitamin A	**Polypeptide** **Glycoproteins** **Catecholamines**
Solubility	**Lipophilic** (able to cross the lipid bilayer of the cells membrane)	**Hydrophilic** in blood (Soluble in the medium)
Transport Proteins	**Yes,** albumin or certain hormones specific binding protein for example the Retinol-binding protein	**No,** because they are soluble
Plasma half-life	**Long (hours – days) =** take very long to clear from plasma Another thing that adds to their longer half life is they are protein bound, so they are more stable in nature	**Short (minutes)**
Receptor	**Intracellular**	**Plasma membrane**
Mediator What is causing the response	**Receptor-hormone complex**	**cAMP, cGMP, Ca 2+, metabolites of complex phospho-inositols, tyrosine kinase cascades** We call these molecules **second messenger**

3

Classification of Hormones by Mechanism of Action

By MOA	
1- Hormones that bind to intracellular receptors	**2- Hormones that bind to cell surface receptors**
Steroid-Thyroid superfamily - Steroid hormones - Thyroid hormones(T3,T4) - Calcitriol - Retinoic acid	1-The second messenger is cAMP 2-The second messenger in cGMP 3-The second messenger is Ca+2 or phosphatidylinositol (or both) 4-The second messenger is a tyrosine kinase cascade

1-Hormones that bind to intracellular receptors

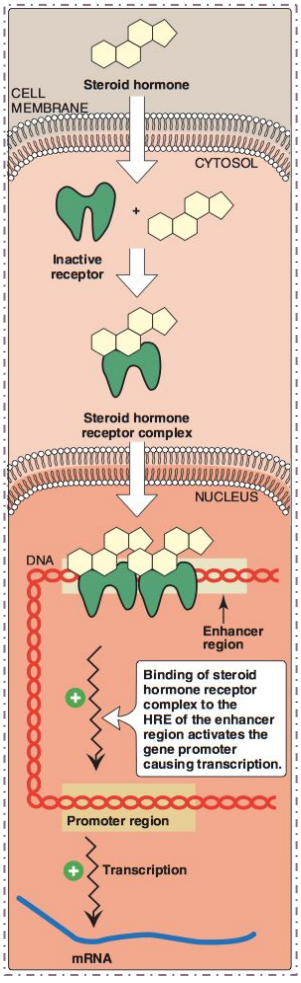
Steroid-Thyroid superfamily

Steroid-Thyroid superfamily	
Calcitriol	**Thyroidhormones**
Active form of vitamin D 1,25[OH]2-D3	(T3 & T4)
Steroid hormones	**Retinoic Acid**
- Glucocorticoids. e.x. Cortisol which involved in glucose metabolism and inflammation. - Mineralocorticoids involved in electrolytes and fluid balance of the body - Sex hormones: 1. Male sex hormones: Androgens 2. Female sex hormones: Estrogens & Progestins	Vitamin A

Act via hormone-receptor complex, which then modifies gene expression.

Within the promoter region of any gene, there are areas which act as enhancers (increase expression of the gene) or repressive (decrease the expression of the gene).

The hormone receptor complex will bind to the enhancer region, and we call this reigning after binding (HRE) hormone response element. Leads to increased expression or transcription of the mRNA of that particular gene.



438 explanation:
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.

4

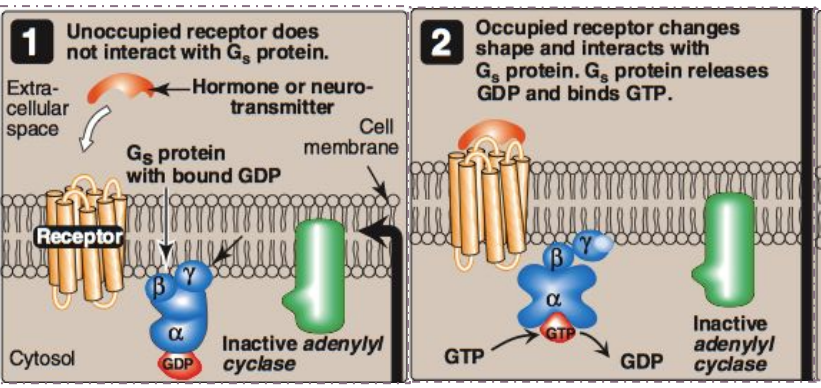
2- Hormones that bind to cell surface receptors

The second messenger is cAMP

Calcitonin & PTH	ADH/Vasopressin	Glucagon	Anterior pituitary	Catecholamines
parathyroid hormone which are involved in the homeostasis of Ca ++ and phosphate	(Renal V2 -receptor) in the kidney. Extrarenal receptor is called V1 receptor.		ACTH, FSH, LH & TSH	α2 - & β- adrenergic receptors : adrenaline and noradrenaline

Cascade for formation of cAMP by cell-surface hormones

438 explanation: 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.



Hormone binds to the G protein coupled receptor (seven helix-transmembrane receptors), activating the G protein.

Note: Inactive G protein has 3 subunits alpha (has GDP), beta and gamma.

When G protein get activated, GDP is replaced by GTP and the alpha subunit is separated from the beta and gamma subunits.

This active G protein (which is alpha subunit bind to GTP) can activate adenylyl Cyclase enzyme. The function of adenylyl Cyclase enzyme is conversion of ATP to cAMP.

Actions of cAMP

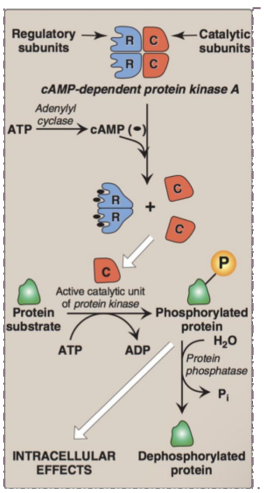
What does cAMP do?

cAMP activates protein kinase A
Protein kinase A has 4 subunits (2 regulatory subunits and 2 catalytic subunits).

The catalytic subunits has the active site of the enzyme which is masked/covered by the regulatory subunits, so the regulatory subunits have to be removed.

When cAMP is produced as second messenger, it binds to the regulatory subunits, which then separate from the catalytic subunits. Now, the protein kinase A is active and can go and do its effects. One of its effect phosphorylation of protein (that will be seen as cellular effect).

When we want to abort this effect, there is different ways to do that. One of the ways is by protein phosphatase which remove phosphate group to become dephosphorylated protein again, so that will stop the response by the cell.

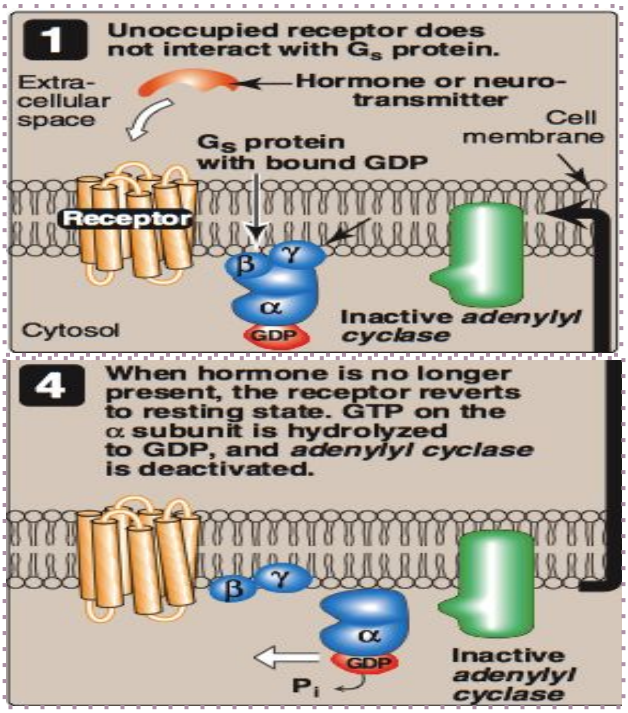


438 explanation:

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.

5 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



Hormones that bind to cell surface receptors

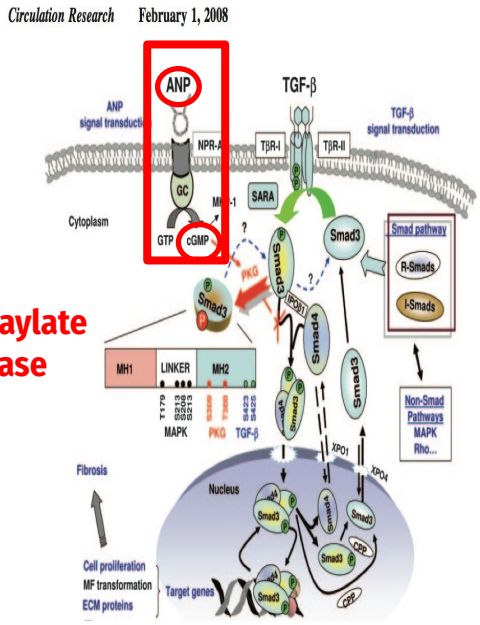
B. The second messenger is cGMP

Atrial natriuretic peptide (ANP)

released when there is volume overload, when the heart muscle are stretched. One of its effect to prevent collagen synthesis that is going to lead to fibrosis

Nitric Oxide

Atrial Natriuretic Peptide (ANP)



GC: Gunaylate cyclase

438 explanation:

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.

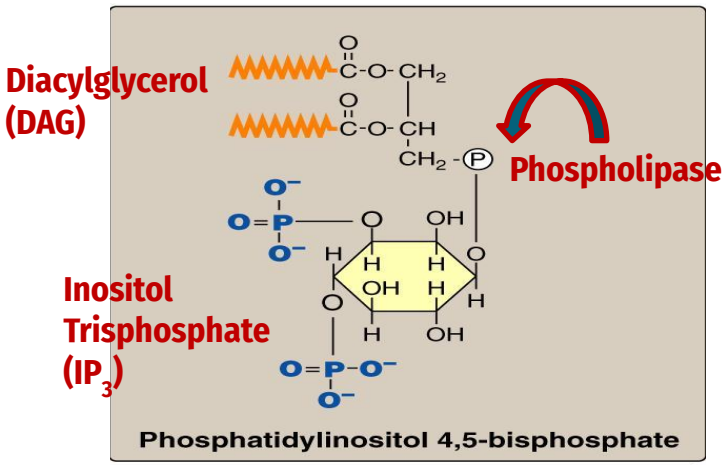
What I want you to know here:

ANP bind to its receptor on cell surface which is NPR-A (Natriuretic Peptide Receptor A) leading to the activation of the enzyme GC (gunaylate Cyclase), the function of this enzyme is to convert GTP into the second messenger cGMP. cGMP activates the enzyme protein kinase G that leads to the biological response.

Hormones that bind to cell surface receptors C. The second messenger is calcium or phosphatidylinositol (or both)			
Acetylcholine	**ADH**	**Angiotensin II**	**Catecholamines**
Muscarinic receptors	**(ExtraRenal V1 -receptor) vasopressin** V2 is via cAMP while V1 is via Ca++ PI	-	**α1 - adrenergic**

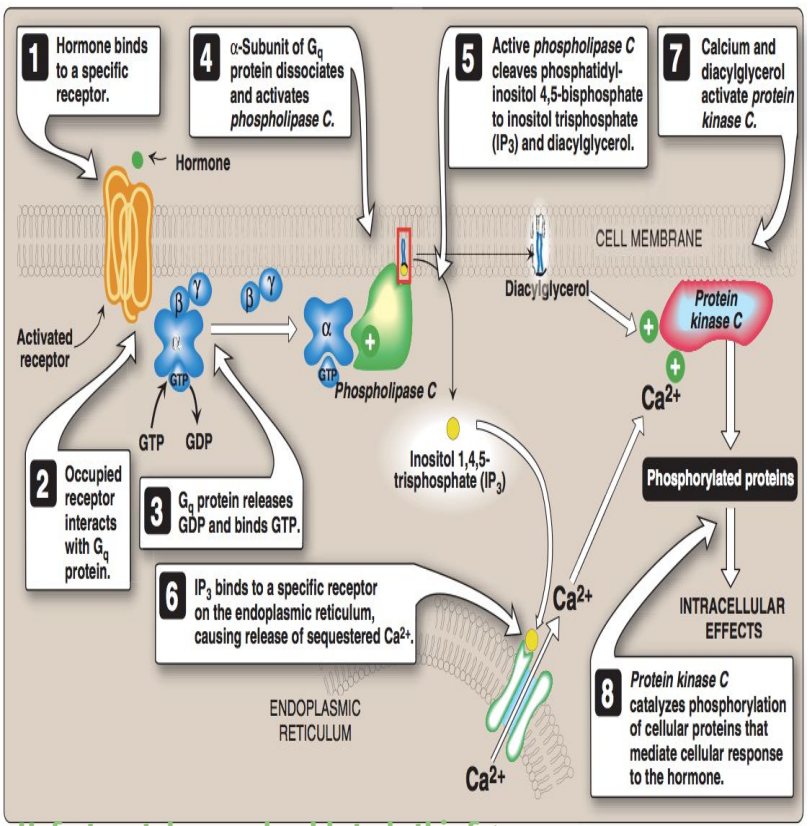
Calcium/Phosphatidylinositol System

helpful videos



Phosphatidylinositol 4,5-bisphosphate
↓ Phospholipase C
Diacylglycerol (DAG) + Inositol phosphate (IP3)

Protein kinase C activation need Ca +2 as a cofactor



Unfortunately, you should study this figure

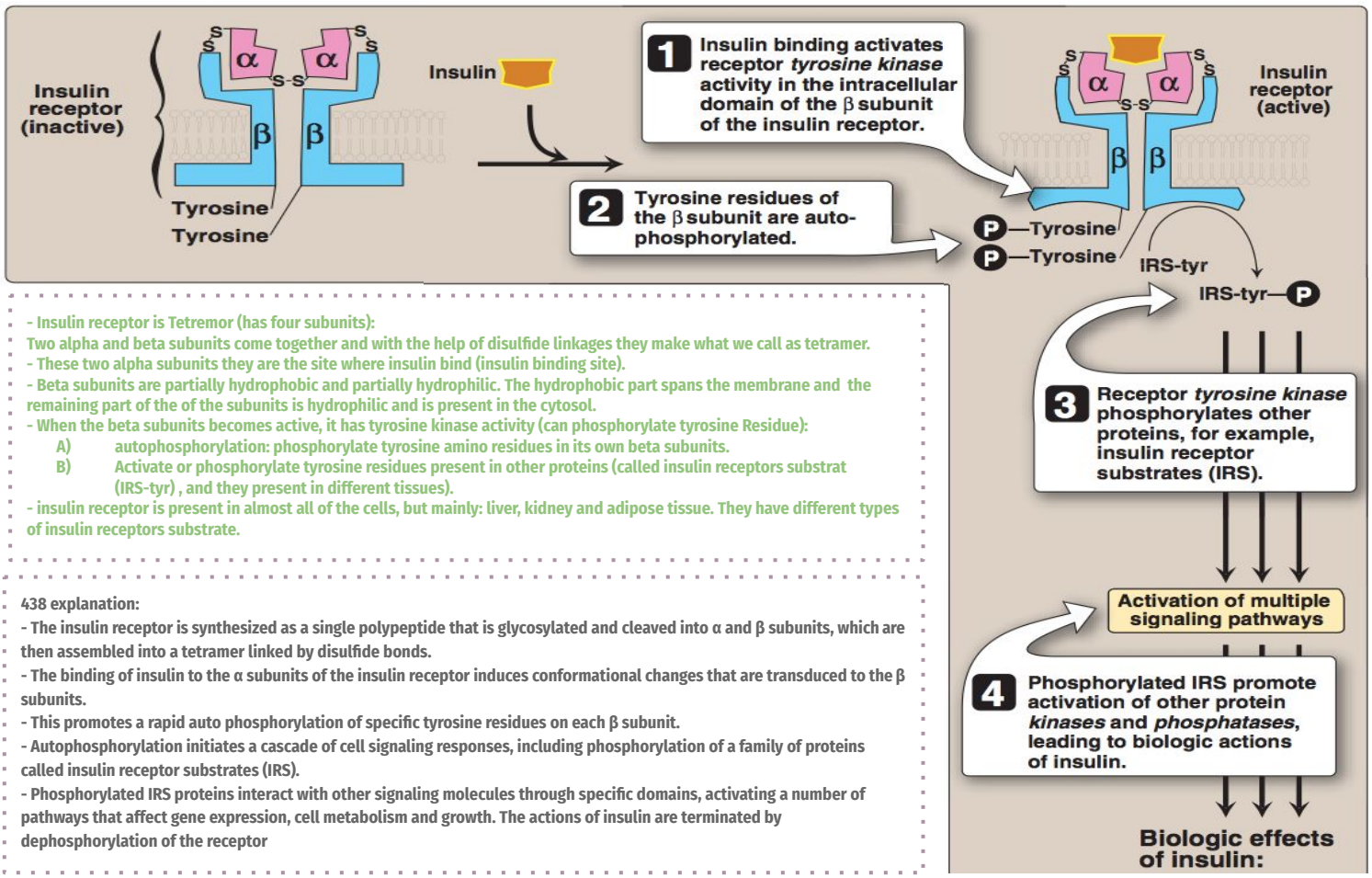
Roles of PI
1- Hormone or neurotransmitter binds to a specific receptor.
2- Occupied receptor interacts with Gq protein.
3- Gq protein releases GDP and binds GTP.
4- α subunit of Gq protein dissociates and activates phospholipase C (enzyme attached to the cell membrane).
5- Active phospholipase C cleaves phosphatidylinositol 4,5-bisphosphate to inositol trisphosphate (IP3) and diacylglycerol.
6- IP3 binds to a specific receptor on the endoplasmic reticulum causing release of sequestered Ca2+
7- Calcium and diacylglycerol activate protein kinase C.
8- Protein kinase C catalyzes phosphorylation of cellular proteins that mediate cellular response to the hormone

7

Hormones that bind to cell surface receptors

D. The second messenger is a tyrosine kinase cascade

- GH & Prolactin
- Insulin
- Erythropoietin



- Insulin receptor is Tetremor (has four subunits):
Two alpha and beta subunits come together and with the help of disulfide linkages they make what we call as tetramer.
- These two alpha subunits they are the site where insulin bind (insulin binding site).
- Beta subunits are partially hydrophobic and partially hydrophilic. The hydrophobic part spans the membrane and the remaining part of the of the subunits is hydrophilic and is present in the cytosol.
- When the beta subunits becomes active, it has tyrosine kinase activity (can phosphorylate tyrosine Residue):
  - A) autophosphorylation: phosphorylate tyrosine amino residues in its own beta subunits.
  - B) Activate or phosphorylate tyrosine residues present in other proteins (called insulin receptors substrat (IRS-tyr) , and they present in different tissues).
- insulin receptor is present in almost all of the cells, but mainly: liver, kidney and adipose tissue. They have different types of insulin receptors substrate.

438 explanation:
- The insulin receptor is synthesized as a single polypeptide that is glycosylated and cleaved into α and β subunits, which are then assembled into a tetramer linked by disulfide bonds.
- The binding of insulin to the α 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

Biologic Effects of Insulin

Increase	Decrease
Glucose uptake	Gluconeogenesis
Protein synthesis	Glycogenolysis
Glycogen synthesis	lipolysis
Fat synthesis	-

These 7 effects are done by: Altered gene expression

Biomedical Importance

1- Excessive (e.g., hyperthyroidism, Cushing), deficient (e.g., hypothyroidism, Addison), or inappropriate secretion (e.g., syndrome of inappropriate secretion (not production) of ADH "SIADH" which leads to retention of water and fluid inside the cells) of hormones are major causes of diseases.

2- 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 Message

1. Hormones are involved in responses to a stimulus, using a variety of signaling mechanisms to facilitate cellular adaptive responses.

2. Group I hormones are lipophilic, while group II are hydrophilic. Other differences exist between both groups.

3. Hormones can be classified according to their mechanism of action (specific examples of each category were discussed)

4. 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

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	
Stimulus	**Group I hormone**	Hormone receptor complex affect: 1- Transport Channels 2-Gene transcription
	Group II hormone	2nd messenger which affect: 1- Transport Channels 2-Gene transcription 3-Protein translocation 4-Protein modification
Classification of Hormones by Mechanism of Action	**I. Hormones that bind to intracellular receptors**	Steroid-Thyroid superfamily: 1- Retinoic acid 2- Thyroid Hormones (T3 & T4) 3- Calcitriol (1,25[OH]2-D3) 4-Steroid hormones: Glucocorticoids Mineralocorticoids Sex hormones: 1- Male sex hormones: Androgens 2- Female sex hormones: Estrogens & Progestin
	II. Hormones that bind to cell surface receptors	**A. The second messenger is cAMP** 1-Catecholamines (α2- & β- adrenergic) 2- Ant. Pituitary: ACTH, FSH, LH & TSH 3- Calcitonin & PTH 4- ADH (Renal V2-receptor) 5- Glucagon **B. The second messenger is cGMP** 1- Atrial natriuretic peptide (ANP) 2- Nitric oxide **C. The second messenger is calcium or phosphatidylinositol (or both)** 1- Acetylcholine (muscarinic) 2- Catecholamines (α1- Adrenergic) 3- Angiotensin II 4- ADH (vasopressin): Extra-renal V1-receptor **D. The second messenger is a tyrosine kinase cascade** 1-GH & Prolactin 2- Insulin (+IGF/Somatomedin) 3- Erythropoietin
Biologic Effects of Insulin	**It decreases**	Lipolysis Gluconeogenesis Glycogenolysis
	It increases	Glucose uptake Glycogen synthesis Fat synthesis Protein synthesis
	How?	Altered gene expression

Test Yourself!

MCQs

Answers: Q1: A | Q2: D | Q3: A | Q4: C

Q1: Hormone that bind to cell surface receptor

A- Catecholamines
B- Mineralocorticoids
C- Thyroid Hormones
D- Calcitriol (1,25[OH]2-D3)

Q2: The cAMP is the second messenger for which hormone?

A- LH
B- FSH
C- NO
D- A&B

Q3: What is the biological effect of insulin on fat synthesis?

A- Increase
B- Decrease
C- Both
D- None

Q4: the Dephosphorylation of protein substrate happen by

A- Adenylyl cyclase
B- Kinase A
C- Phosphatase
D- βγ-subunits

SAQs

Q1- list the biological effect of insulin

A: Slide 9

Q2- list the Factors determining the response of a target cell to a hormone

A: Slide 3

Meet The Team!

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