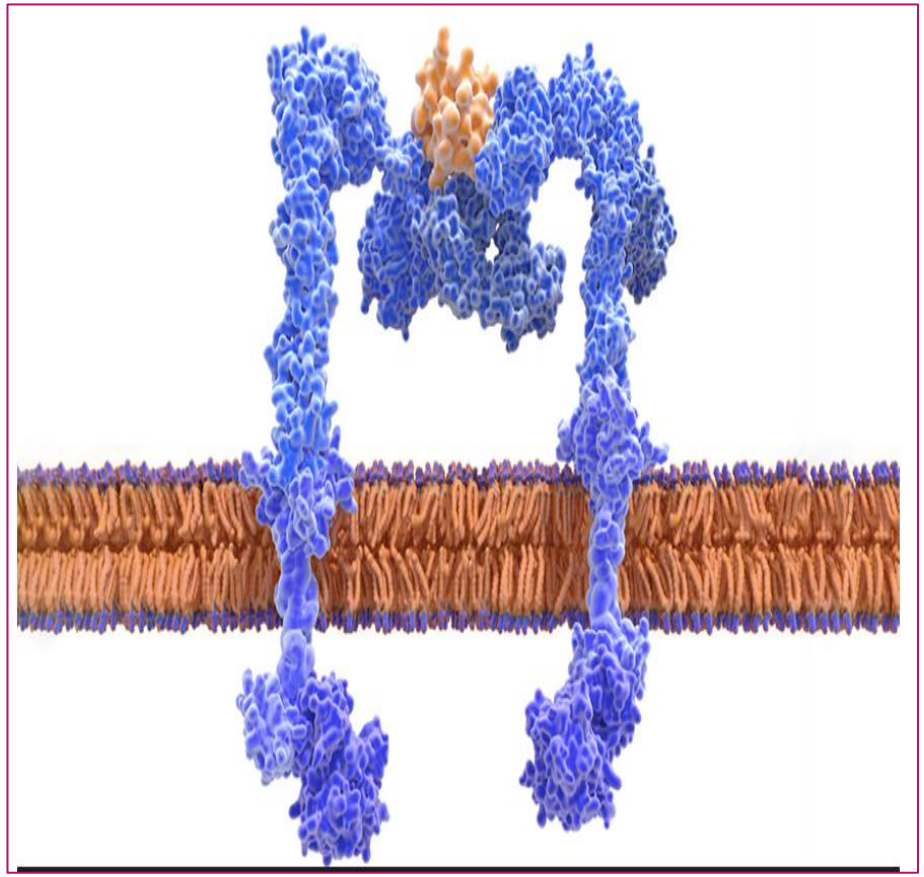

Introduction to Hormone Structure and Ligand Receptors Interactions

Presented By :
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Learning outcomes

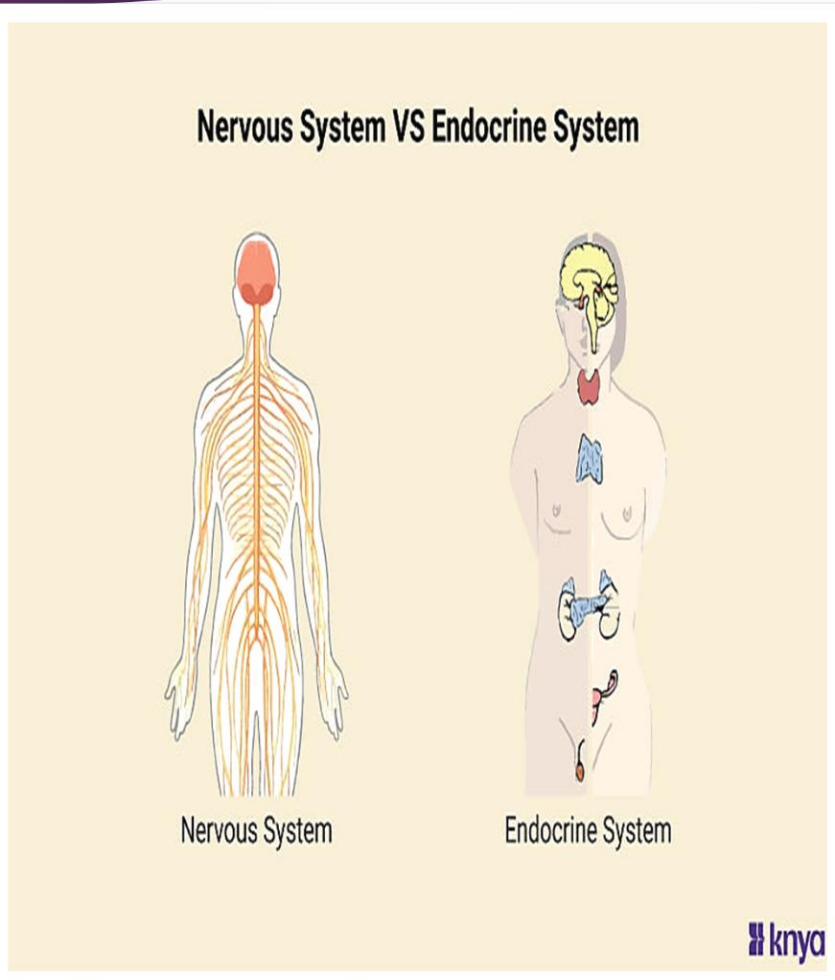
At the end of this lecture, students should be able to:

1. Define hormones, target cells, and hormone receptors
2. Identify cellular location and functional sites of hormone receptors
3. Classify hormones according to its chemical structure and solubility
4. Explain how hormones exert their effects through receptors and intracellular signaling pathways.
5. Summarize the role of cAMP, cGMP, calcium , phosphatidyl inositol, tyrosine kinase and ca as 2nd messenger.

Contents

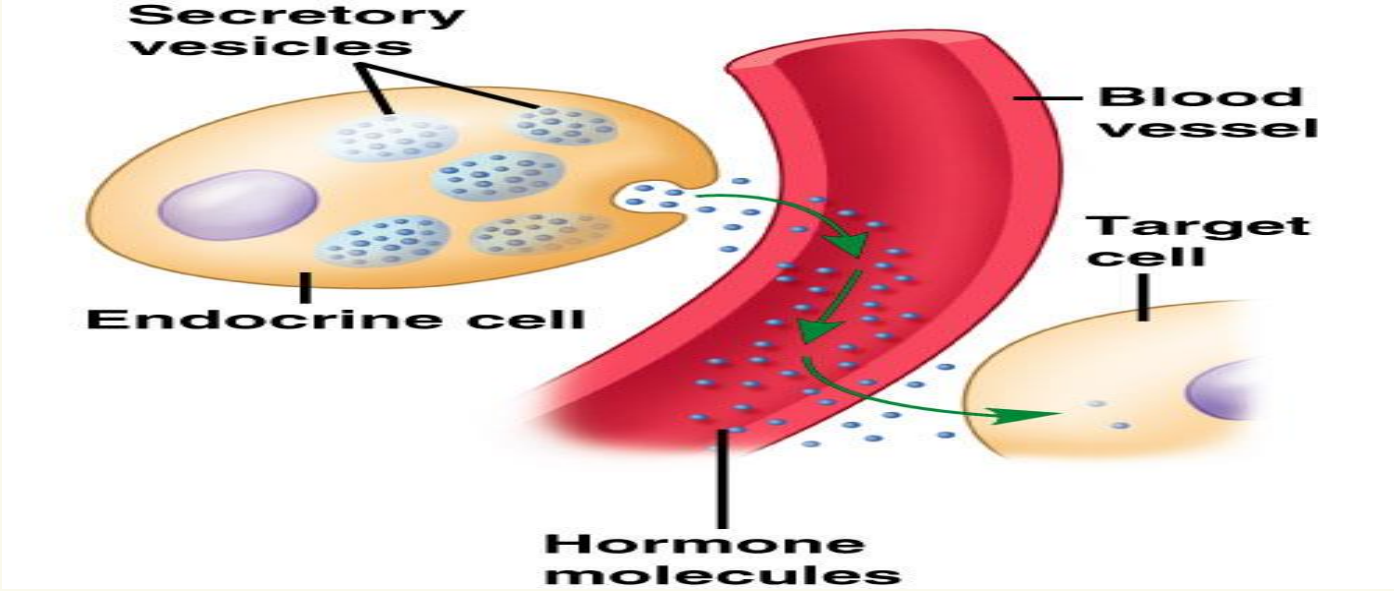
Introduction

- Two systems coordinate communication throughout the body:
  - The **endocrine system** secretes hormones that coordinate slower but longer-acting responses including reproduction, development, energy metabolism, growth, and behavior.
  - The **nervous system** conveys high-speed electrical signals along specialized cells called neurons; these signals regulate other cells.



I. Hormones

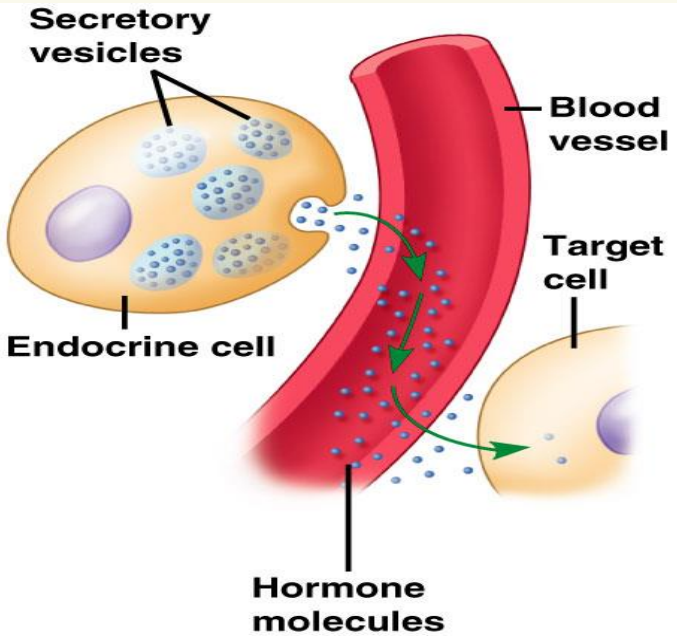
Hormones are chemical signals that are secreted into the circulatory system and communicate regulatory messages within the body.

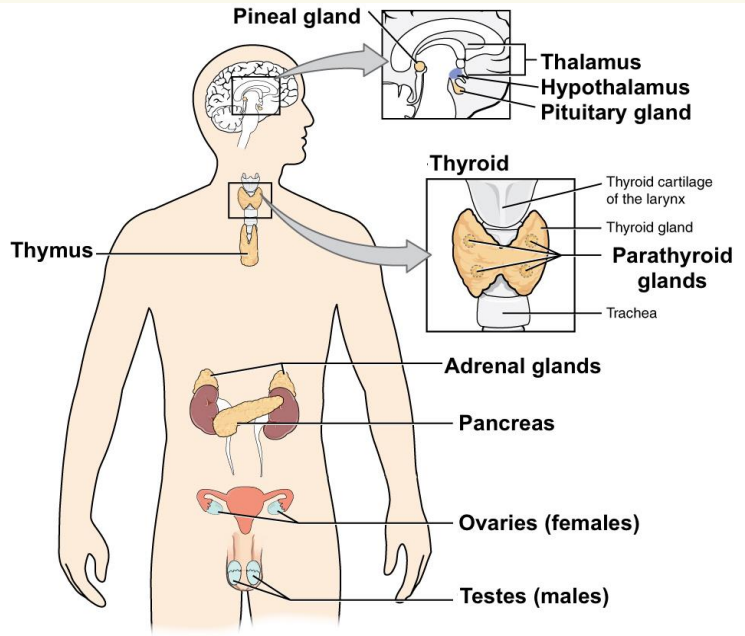


I. Hormones

-They are natural **organic** substances, secreted from the ductless **glands** into the blood.

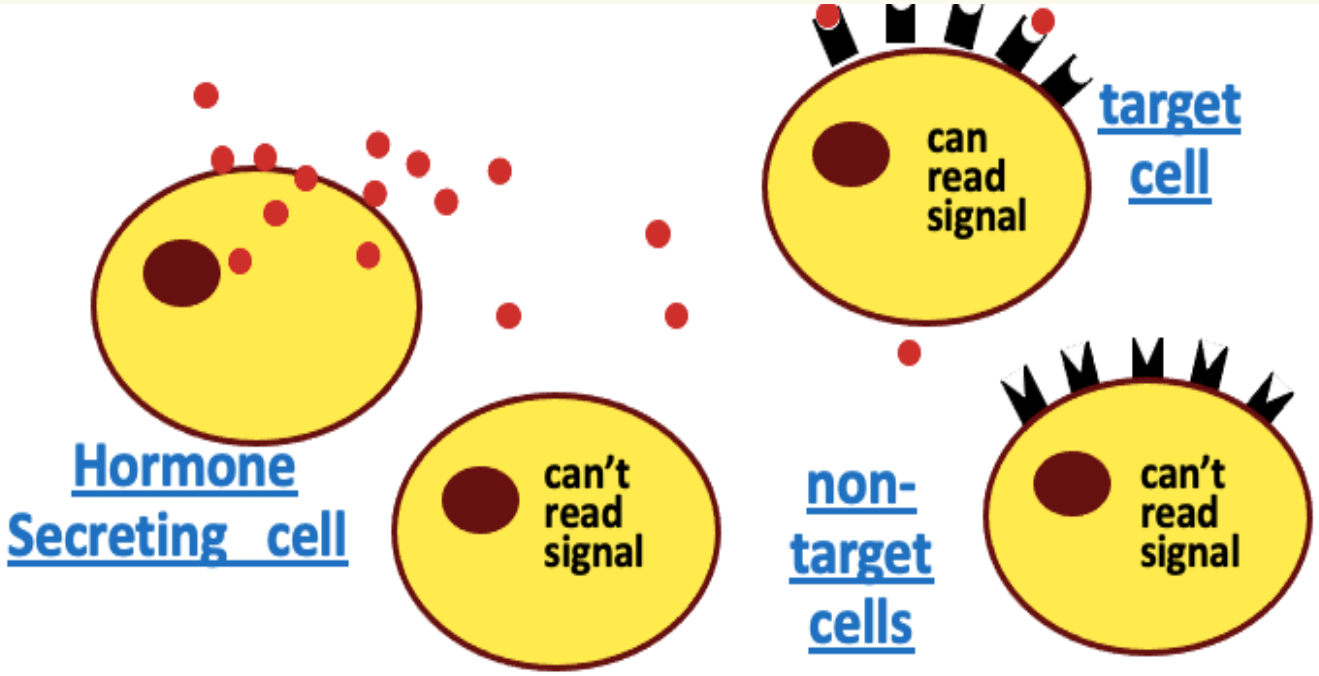
- Hormones reach all parts of the body, but only target cells can respond to signals.





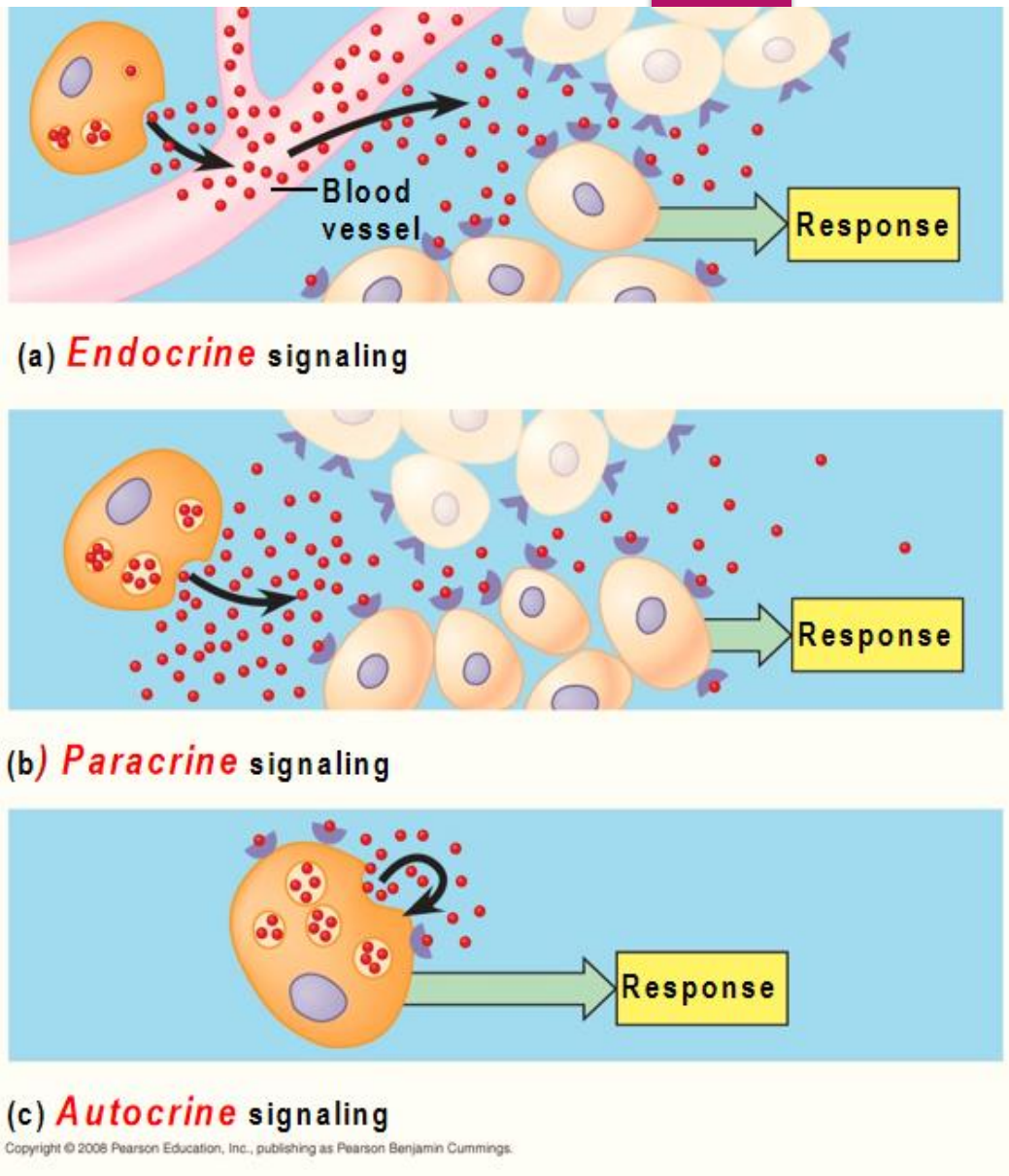
II. Target cell

- It is the cell that contains the specific receptors of the hormone.
- hormone fits receptor on target cell like a lock and a key



Local Regulators = Short Distance Chemical Signals

- Local regulators are chemical signals that travel over short distances by diffusion.
- Local regulators are divided into two types:
  - Paracrine signals act on cells near the secreting cell.
  - Autocrine signals act on the secreting cell itself.



Intercellular communication by secreted molecules

III. Hormone receptors

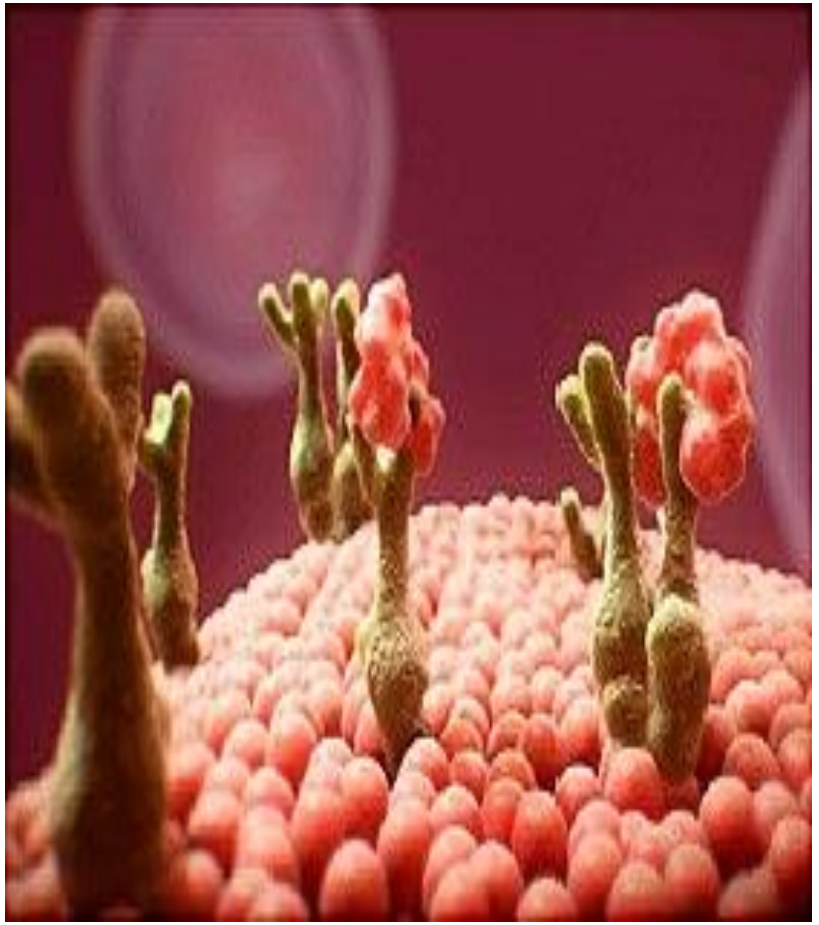
1. Definition

2. Functional sites

3. Cellular location

1- Definition

- They are cell-associated recognition molecules.
- They are protein in nature.



2. Functional sites

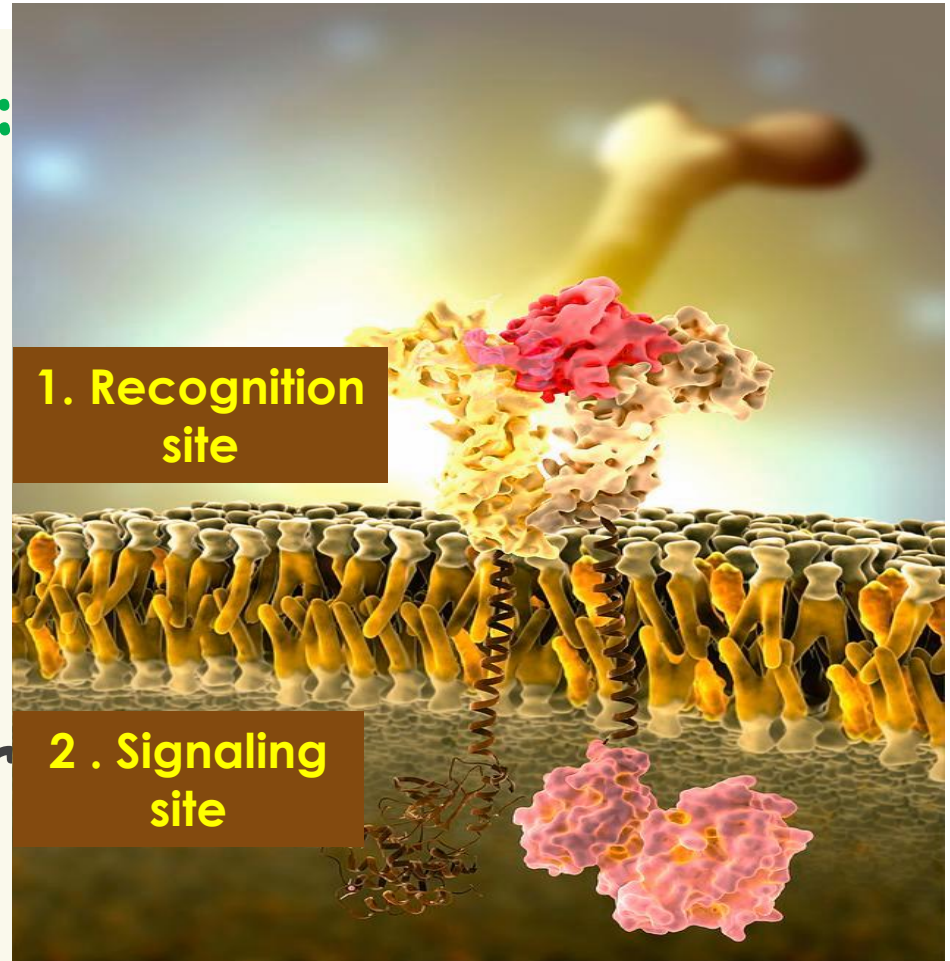
- Each receptor has two functional sites:

1. Recognition site:

it binds the hormone specifically.

2. Signaling site:

it couples hormone binding to intracellular effect.



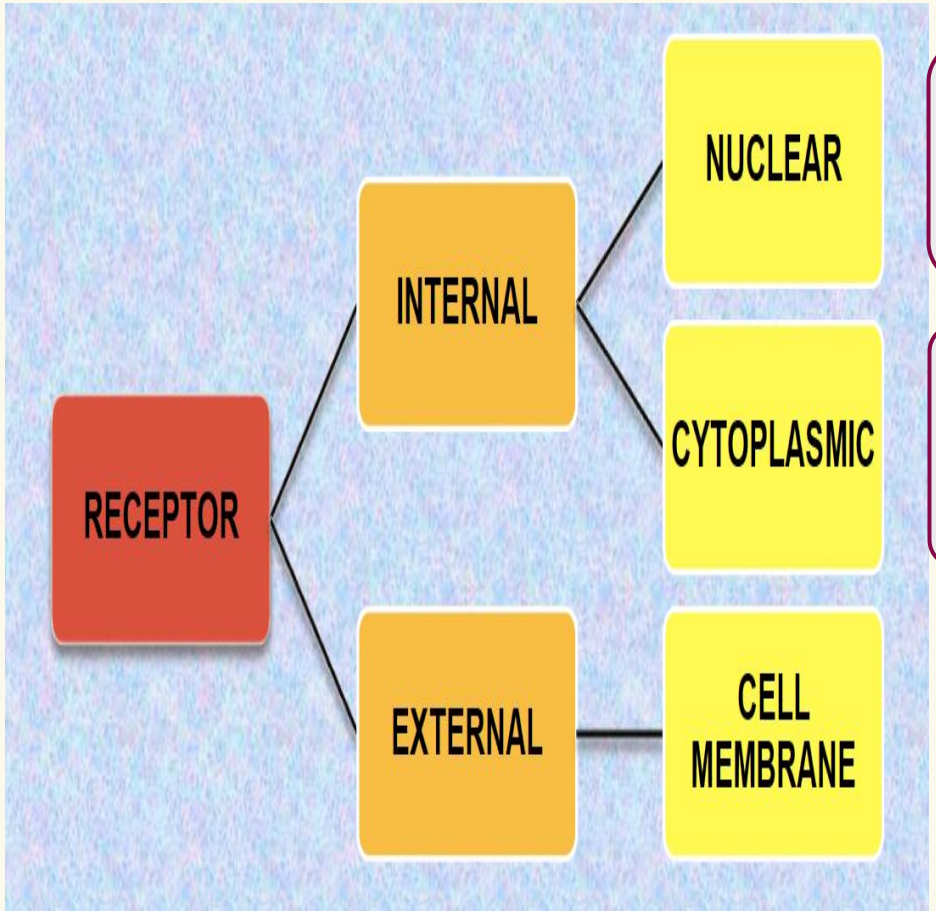
3. Cellular location

1. Intracellular receptors:

Located inside the cell either in the cytosol or in the nucleus.

2. Cell-membrane receptors:

Located in the plasma membrane of the cell.



IV. Classification of Hormones:

1. Classification according to the chemical nature

A) Steroid hormones
B) Non steroid hormones

2. Classification according to the solubility

A) Lipophilic hormones
B) Hydrophilic hormones

1. Classification according to the chemical nature

A) Steroid hormones:

✓ They are derived from cholesterol.

1. Glucocorticoids
2. Mineralocorticoids.
3. Sex hormones: -Androgens (testosterone),
   -Estrogens,
   -Progesterone

1. Classification according to the chemical nature

B) Non steroid hormones

I. Protein Hormones:

1.Large polypeptides: -e.g. Growth hormone, Insulin & Glucagon

2.Small polypeptides:- e.g. ADH (9 a.a.), oxytocin (9 a.a.)

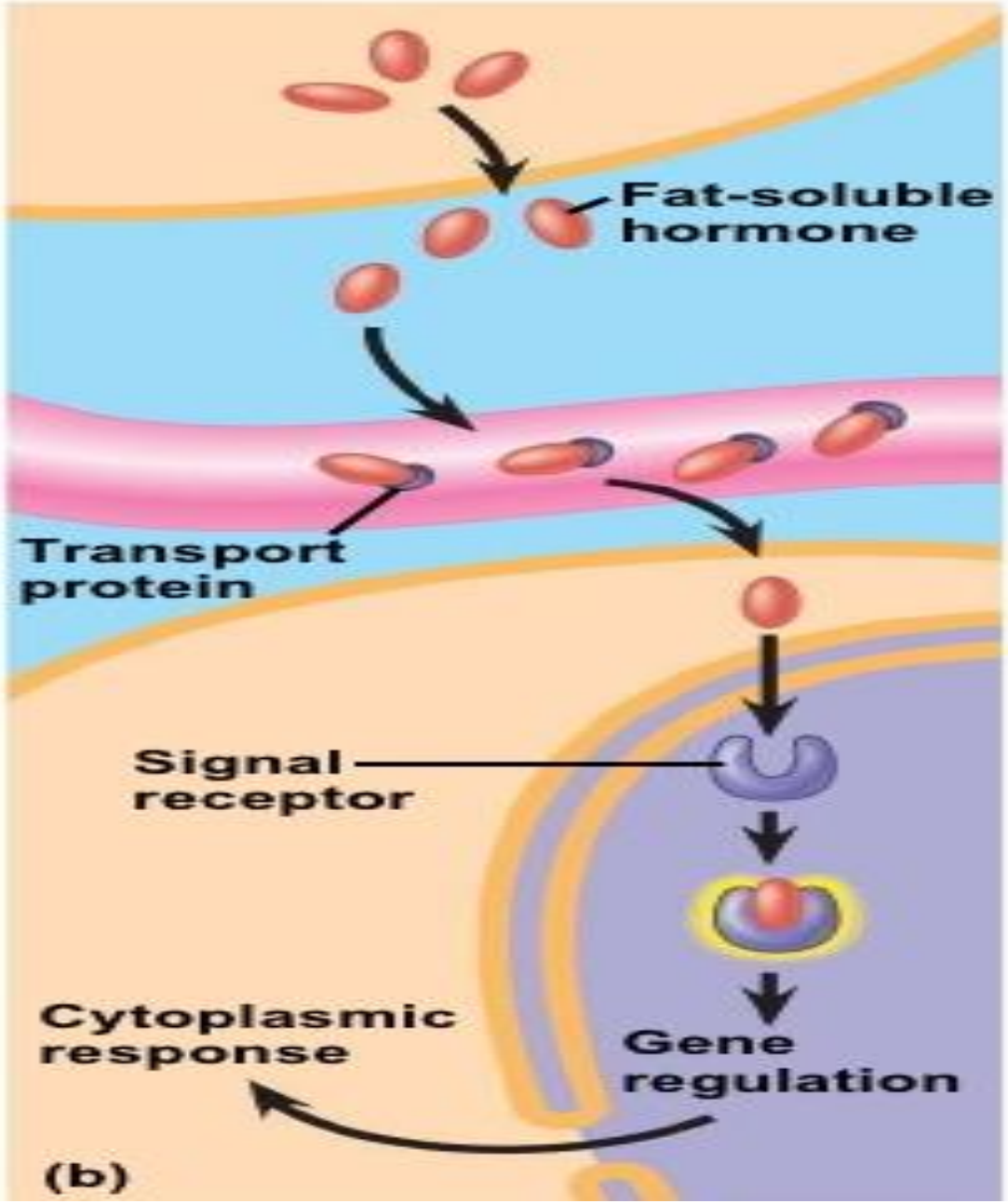
3.Glycoprotein hormone: e.g- e.g. FSH - LH – TSH- HCG

II. Amino Acid Derived Hormones: hormones derived from amino acids.

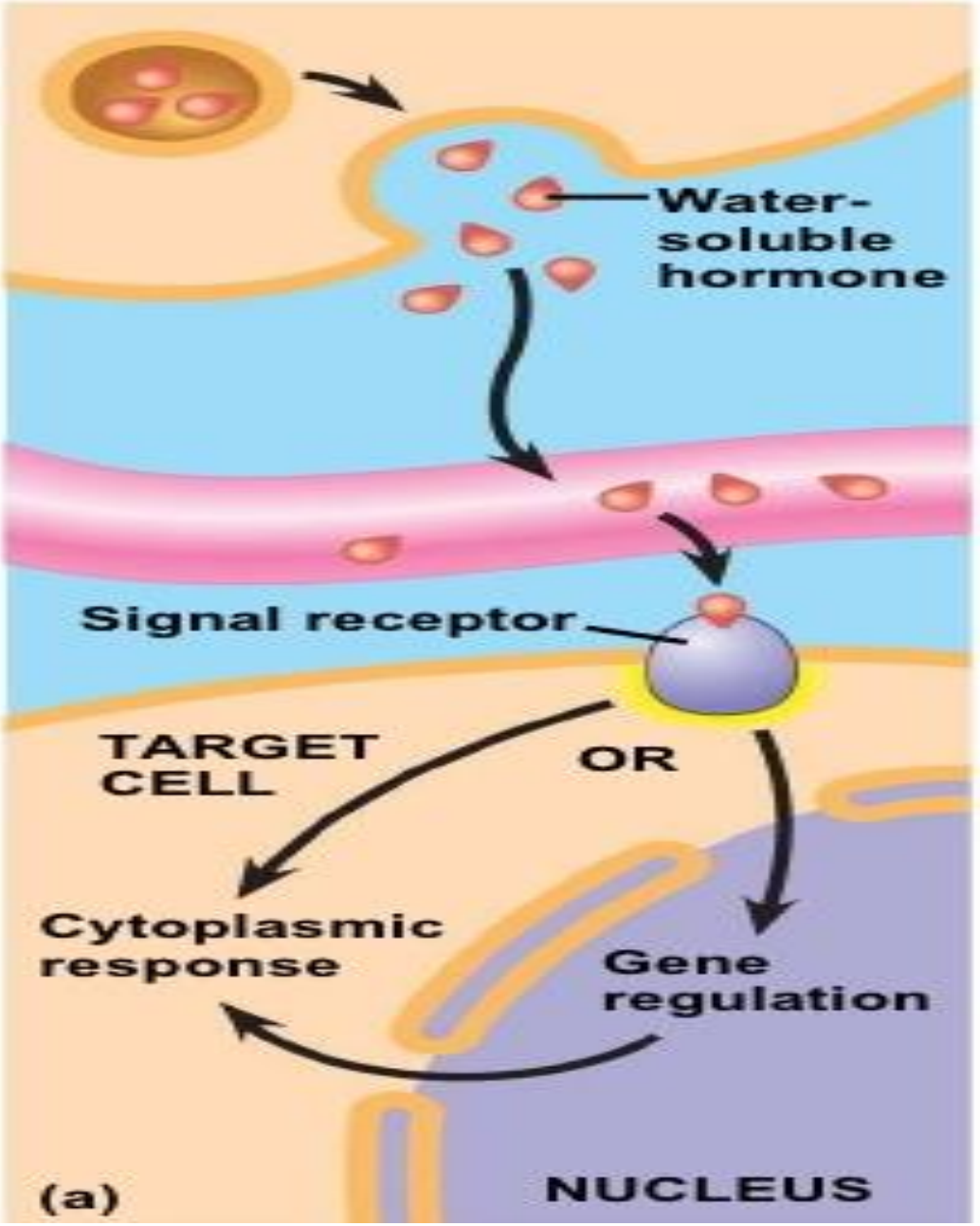
- Thyroid hormones, adrenaline, noradrenaline from Tyrosine AA
- Melatonin from Tryptophan AA

2. Classification according to the solubility

	Lipophilic hormones	Hydrophilic hormones
Solubility	Fat soluble	Water soluble
Example	Steroid and thyroid hormones	Proteins, peptide hormones & catecholamines
secreted by	secreted by exocytosis	secreted by diffusion (across cell membranes)
Transport in plasma	Bound to plasma protein	Free (no need to bind plasma protein)
Target cell	Penetrate plasma membrane	Can not penetrate pl. membrane
Receptor	Intracellular	Cell membrane



Intracellular receptors



Cell membrane receptors

2. Classification according to the solubility

	Lipophilic hormones	Hydrophilic hormones
Mechanism of action	Binding with receptors in the nucleus or cytoplasm→ activates or inhibits gene transcription→ **Change the enzyme amount**	Phosphorylation reaction →↑ or↓ enzyme activity i.e. **Change the enzyme activity**
Response	Slower response, takes hours (a change in gene expression)	Fast response, takes minutes
Mediator	Action is mediated by forming **hormone-receptor complex.**	Action is mediated by **Second messenger**

V. Mechanisms of Hormonal Action

A. Hormones, which bind to intracellular receptors

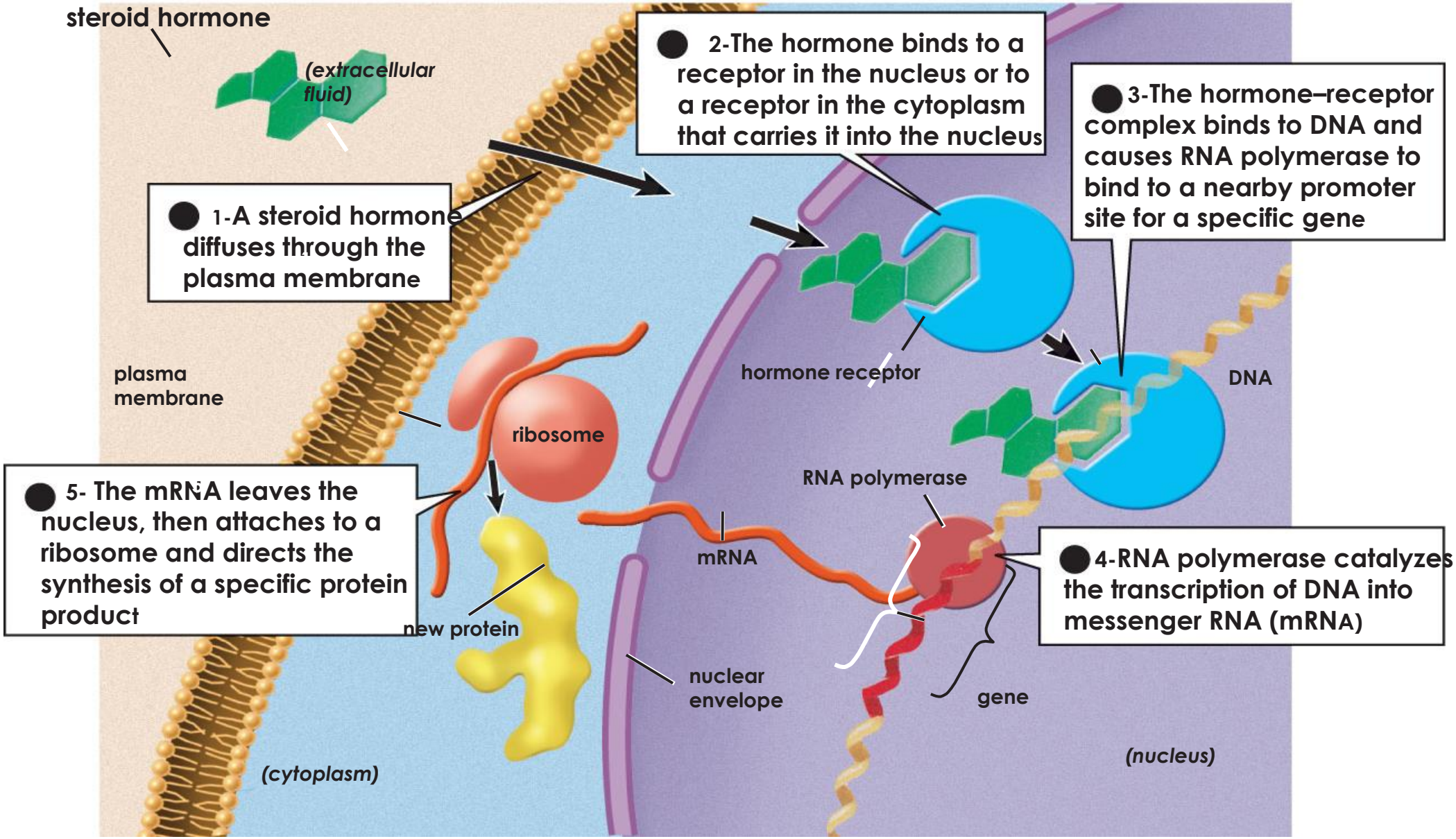
B. Hormones, which bind to membrane receptors

A. Hormones which bind to intracellular receptors

- ✓ For lipophilic hormones (**Steroid hormones, Thyroid hormones**) (**all act as nuclear transcription factors**)
- ✓ These hormones are transported in blood **bound to plasma proteins**
- ✓ Being fat soluble, it **penetrates** the phospholipid bilayer of the cell membrane→ Then **binds to a receptor** in the nucleus or cytoplasm that carries it to the nucleus.

A. Hormones which bind to intracellular receptors

- ✓ Then the **hormone-receptor complex binds** to DNA sequence called **hormone response element (HRE)** → affects RNA polymerase binding to specific gene → **transcription of DNA** into mRNA→ mRNA leaves the nucleus to cytoplasm → translation → directs the synthesis of a specific protein (enzyme) product → **change the amount of enzyme**



Steroid hormone receptors and mechanism of action

Mechanism of Thyroxine Action

Thyroxine is a water-insoluble hormone that is brought to the target cell via a protein carrier. Because it is lipophilic, thyroxine can easily pass through the cell membrane.

B. Hormones, which bind to membrane receptors.

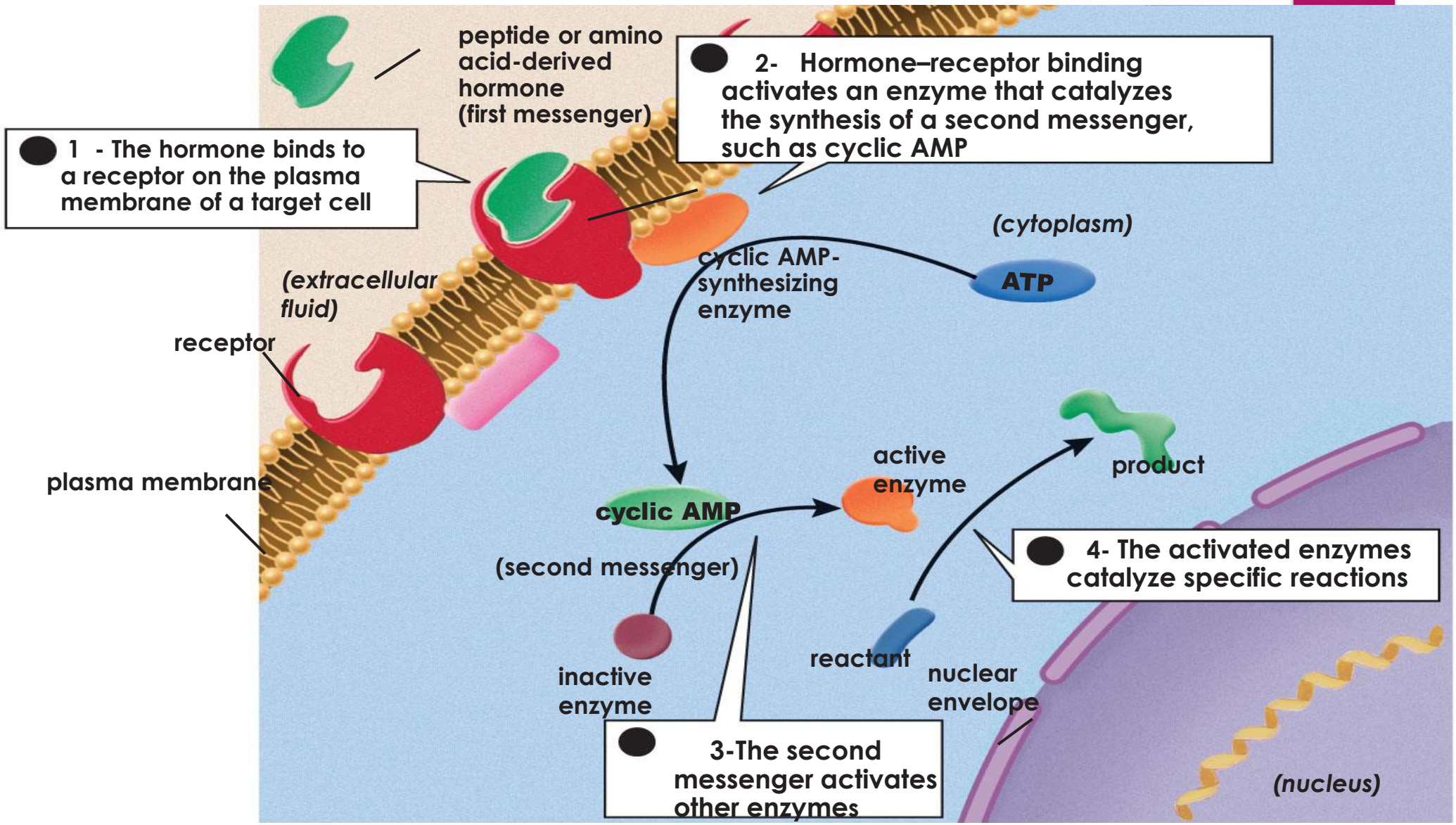
- For Hydrophilic hormones like:

  Protein hormones, peptide hormones, and catecholamines.

- These water-soluble hormones (first messenger)→ Circulate mainly **dissolved** in the plasma→ reach to the target cells but cannot penetrate the membrane as it is not fat soluble→ so it **binds to receptor** proteins in the **cell membrane.**

B. Hormones, which bind to membrane receptors.

- ✓**This Hormone-receptor binding** → activates an enzyme that catalyzes the synthesis of a **second messenger** (a signal produced as a result of hormone binding to its cell membrane receptor)
- ✓This 2nd messenger activates **other enzymes** that catalyze a specific reaction in the cell→ mediate the hormone action. **(it changes the enzyme activity)**
- ✓**NB. Hormone itself acts as first messenger.**



Peptide hormone receptors & mechanism of action

VI.
The Second Messenger

- Cyclic AMP (cAMP)
- Cyclic GMP (cGMP)
- Ca & PI
- Protein (Tyrosine) kinase cascade

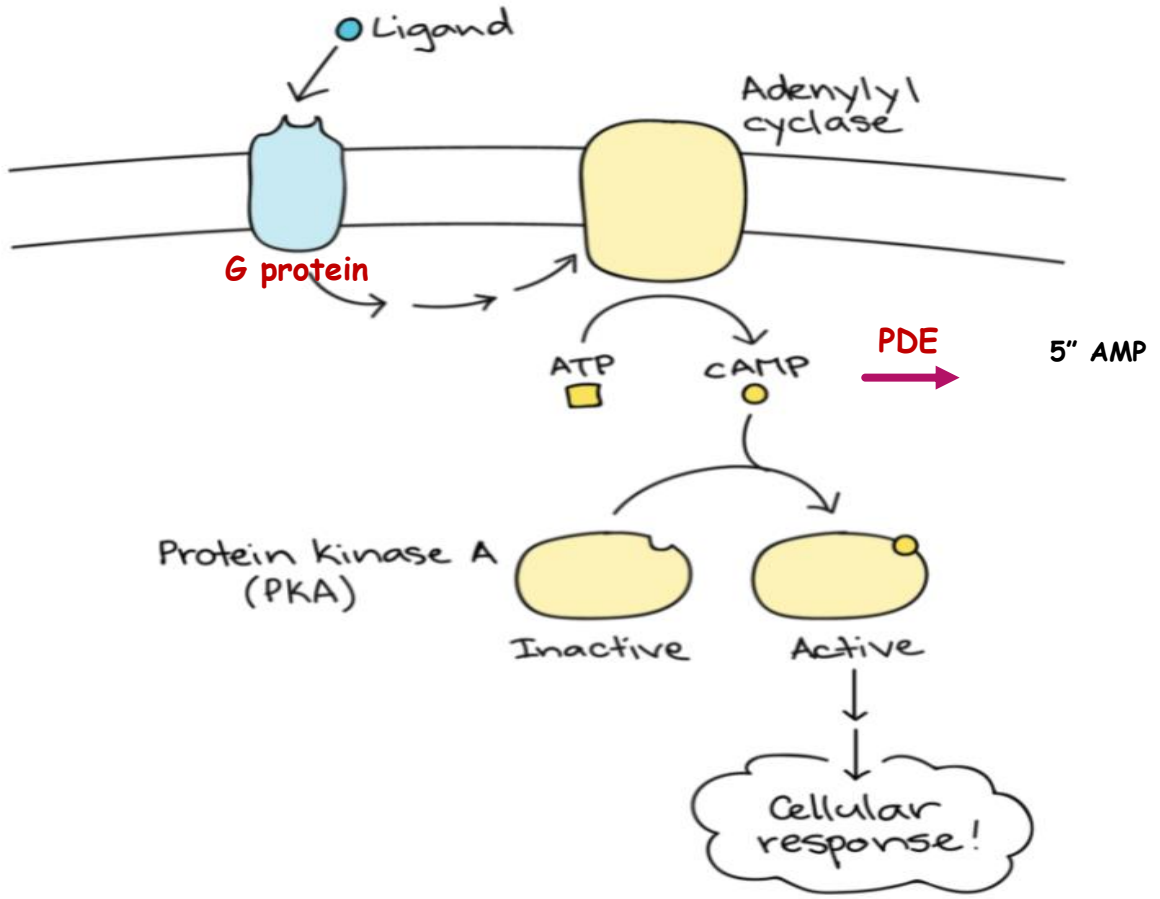
The Second Messenger

- ✓It is the signal produced as a result of hormone binding to its cell membrane receptor.
- ✓It mediates the effects of the hydrophilic hormones.
- ✓The hormone itself is considered as the first messenger.
- ✓The second messenger may be:
    i. Cyclic Adenosine Monophosphate (cAMP).
    ii. Cyclic Guanosine Monophosphate (cGMP).
    iii. Calcium or phosphatidyl inositides (PIs) or both.
    iv. Protein kinase cascade.

1- Cyclic AMP as a 2nd messenger

1. Some hormones like **catecholamines, glucagon** utilize cAMP as 2nd messenger

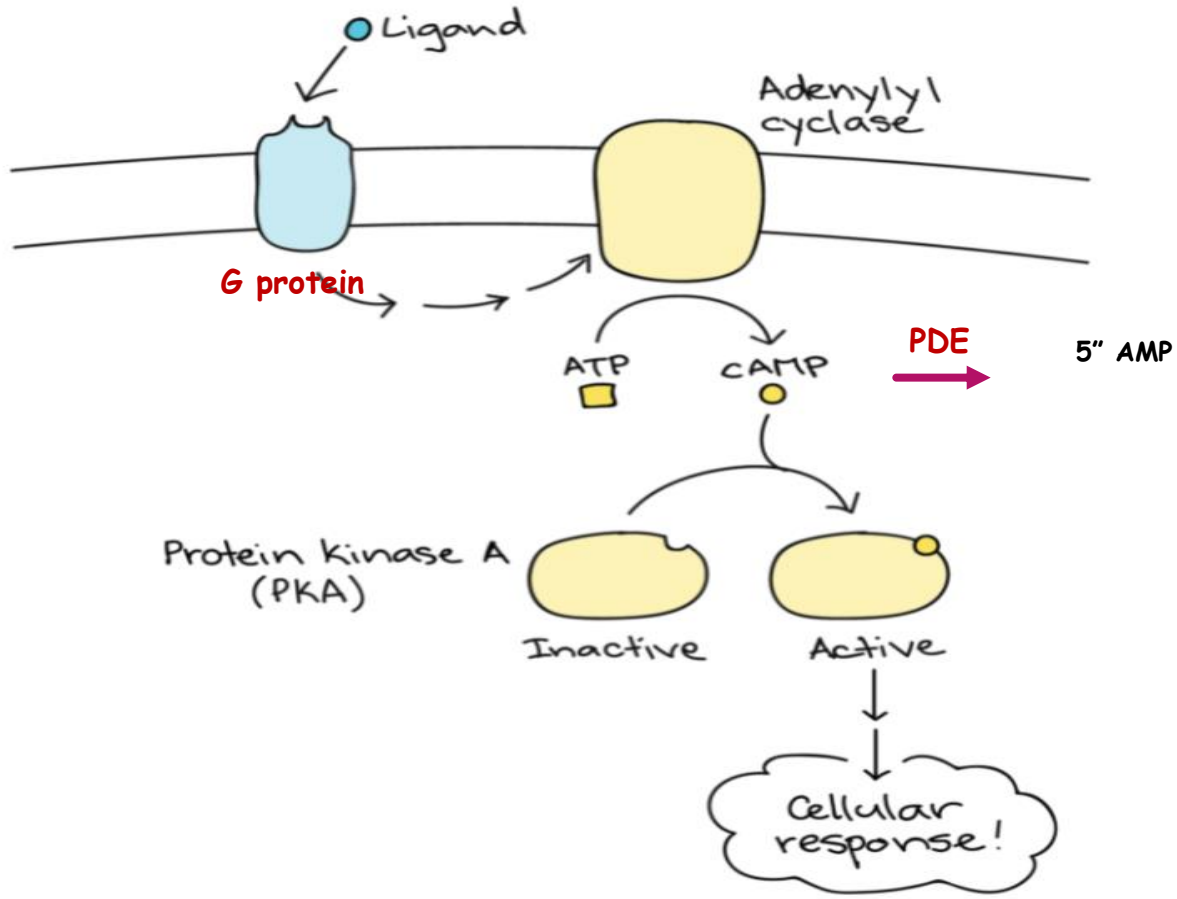
1. Binding of the hormone (ligand) to cell membrane receptor→ activates **regulatory protein (G protein)**→ activates **adenylate cyclase enzyme**→ catalyzes the formation of **cAMP** from ATP.



1- Cyclic AMP as a 2nd messenger

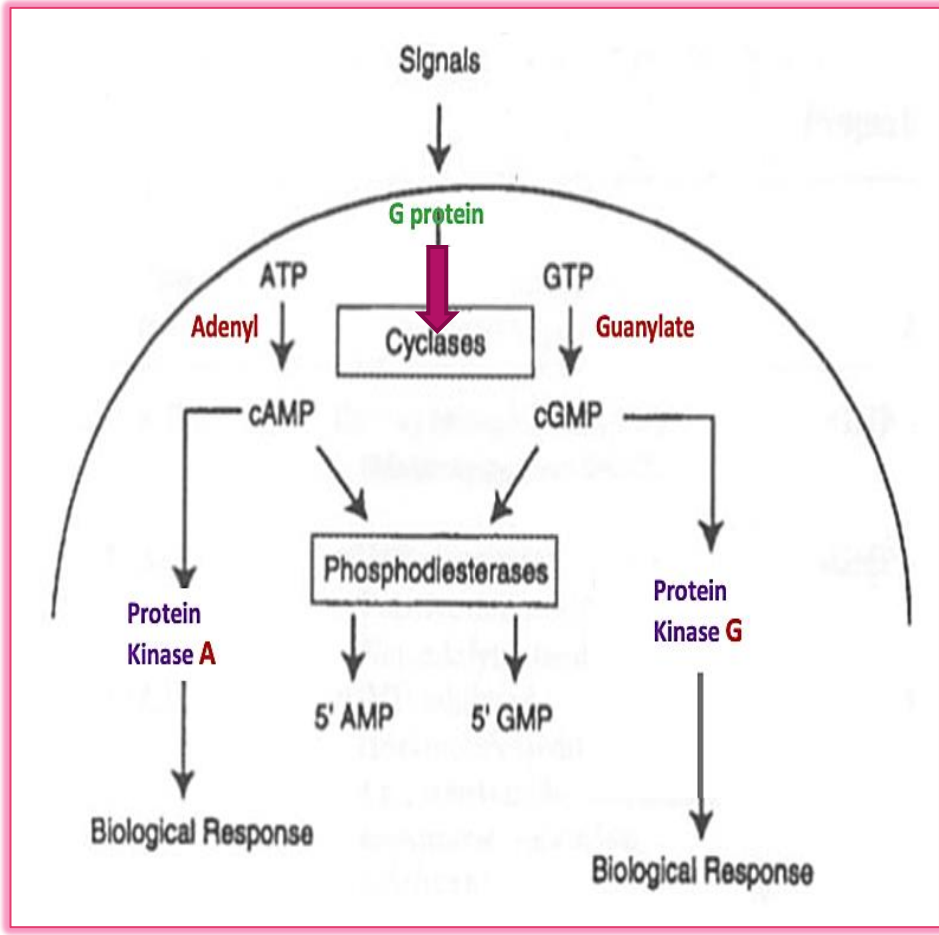
3. Then cAMP→ Activates **protein kinase A** →Phosphorylation of certain enzymes

4. Then **phosphodiesterase enzyme (PDE)** hydrolyses cAMP to 5' AMP and stop its action.



2-Cyclic GMP as a 2nd messenger

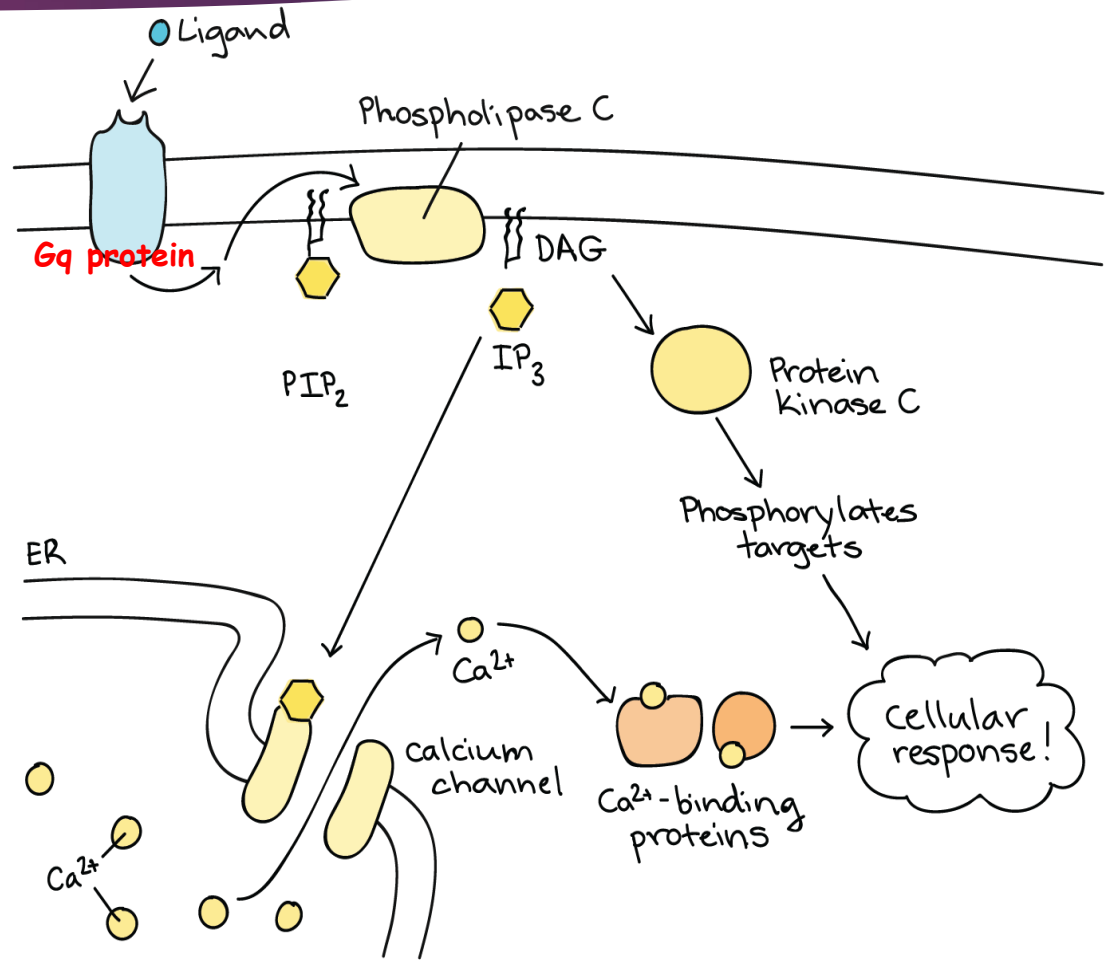
- ✓ It is the 2nd messenger of Atrial natriuretic factor **(ANF)** that is produced in cardiac atrial tissues.
- ✓ The hormone binds to its specific receptor→ activates guanylate cyclase → catalyzes the transformation of GTP to cGMP→ cGMP activates protein kinase G→ protein phosphorylation→ mediates the effects of ANF (**smooth muscle relaxation, vasodilatation**)
- ✓ After mediating its effects, cGMP is hydrolyzed by phosphodiesterase enzyme to **5' GMP**.



3-Calcium or phosphatidyl inositol as 2nd messenger

1. Some hormones like: **GnRH, TRH, ADH** use these second messengers.
2. Binding of the hormone (ligand) to its specific receptor → activates **G protein (Gq)** → activates the enzyme **phospholipase C (PLC)**→ The active PLC hydrolyses **phosphatidyl inositol bi biphosphate (PIP2) to:**

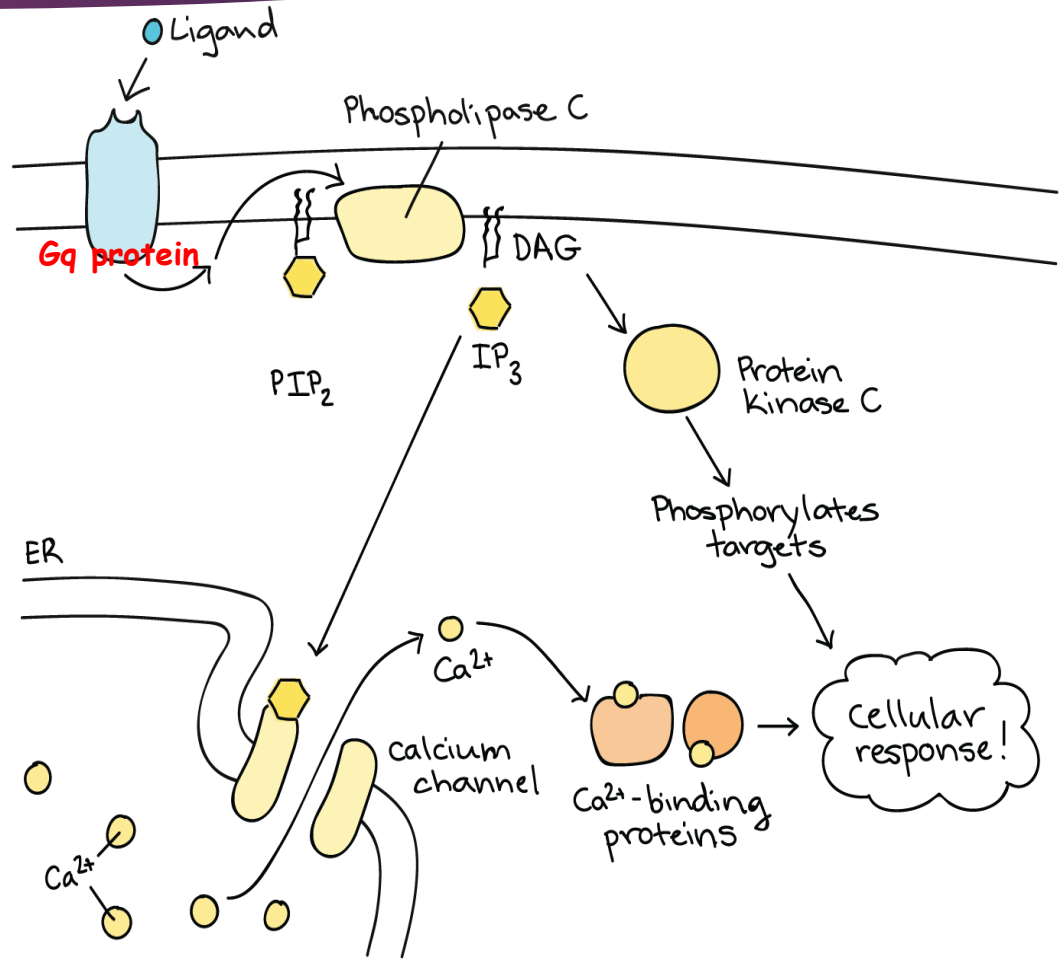
    1. Diacyl glycerol (DAG)→
    2. Inositol Triphosphate (IP3)→



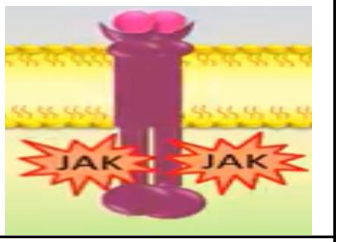
3-Calcium or phosphatidyl inositol as 2nd messenger

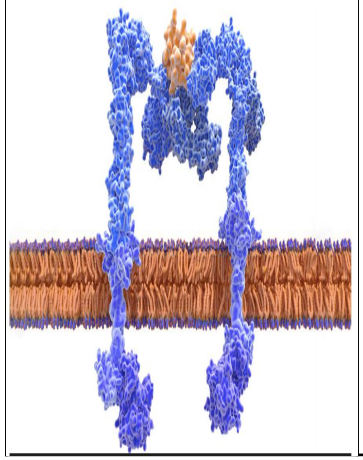
1. Diacyl glycerol (DAG)→It activates protein kinase C→ phosphorylation of enzyme/protein → mediate the effects of the hormone.

2. Inositol Triphosphate (IP3)→ releases Ca2+ from intracellular storage sites (ER , Mitochondria) → Ca^{2+} binds to Ca binding protein (calmodulin) → change activity of certain enzymes → mediate the effects of the hormone.



4- Tyrosine kinase as a 2nd messenger

Tyrosine kinases:	are group of enzymes, which phosphorylate their substrates on tyrosine residues.	
Tyrosine kinases may be:	**a) Intrinsic part of the receptor.** 	**b) Intracellular associated (coupled) with the receptor but not an intrinsic part of it** 
Example	Insulin: (IRS)	Growth hormone :(JAK/STAT)
Mechanism	Insulin binds to its receptor ↓ activates the receptor's intrinsic tyrosine kinase activity ↓ **Autophosphorylation** of tyrosine residues of the receptor ↓ Activation of **insulin receptor substrate (IRS)** → activation cascade ↓ Mediate **effects of insulin**	Growth hormone binds to its receptor ↓ **Activation of associated** tyrosine kinase **Janus Kinase (JAK),** ↓ Activation of **STAT** → Activation cascade ↓ Activation of **transcription**



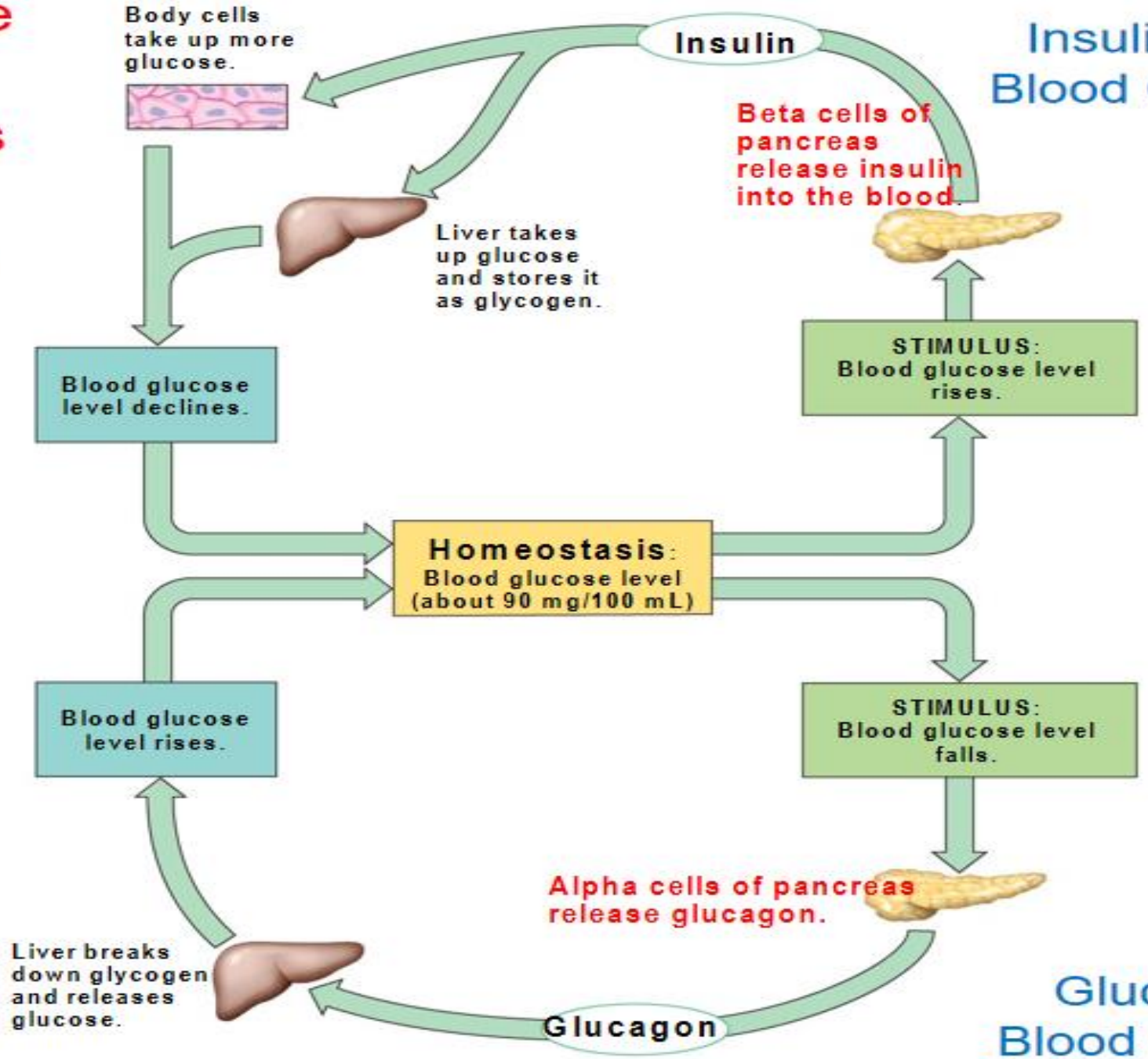
A) Insulin hormone: intrinsic tyrosine kinase receptor

B) Growth hormone: intracellular associated tyrosine kinase receptor

Example for Simple Hormone Pathways:
Insulin and Glucagon: Control of Blood Glucose

- **Hormones** are released from an **endocrine** cell, travel through the **bloodstream**, and interact with the **receptor** or a **target cell** to cause a **physiological response**.
- **Insulin** and **glucagon** are **antagonistic hormones** that help maintain glucose homeostasis.
- The **pancreas** has endocrine cells called **islets of Langerhans** with *alpha cells* that produce glucagon and *beta cells* that produce insulin.

Maintenance of glucose homeostasis by insulin and lucagon



Insuline decreases Blood Glucose Levels

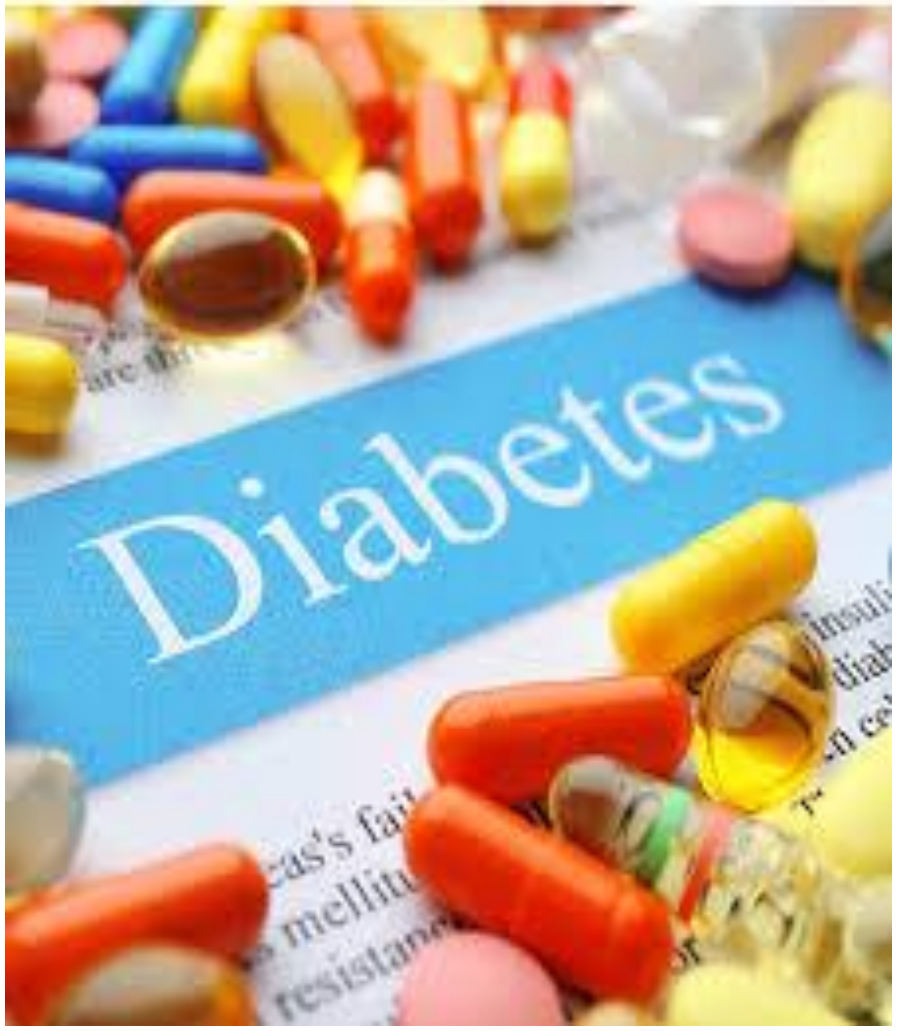
Glucagon Raises Blood Glucose Levels

Target Tissues for Insulin and Glucagon

- ***Insulin reduces blood glucose levels*** by
  - Promoting the cellular uptake of glucose
  - Slowing glycogen breakdown in the liver
  - Promoting fat storage.
- ***Glucagon increases blood glucose levels*** by
  - Stimulating conversion of glycogen to glucose in the liver
  - Stimulating breakdown of fat and protein into glucose.

Diabetes Mellitus

- **Diabetes mellitus** is an endocrine disorder caused by a deficiency of insulin or a decreased response to insulin in target tissues.
- It is marked by elevated blood glucose levels.



Summary

Hormones are natural organic substances, secreted from endocrine glands into the blood and affect target tissues

Hormone fits to the receptor on target cell like a lock and a key

Hormone receptors are protein in nature, each receptor has two functional site; recognition and signaling sites

Hormones may be steroid or non steroid in nature, act on either cell membrane receptors or intracellular receptors

Hormone action is mediated by forming hormone-receptor complex that stimulate gene expression Or act via 2nd messenger

References

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- Lippincott’s Illustrated Reviews: Biochemistry, 8th edition
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- Vasudevan's Textbook of Biochemistry For Medical Students, 6th Edition.


Life
isn't about
finding yourself.
...
Life
is about
creating yourself.