Tishk International University
Faculty of Science
Department of Medical Analysis

## ADVANCED CLNICAL BIOCHEMISTRY

# Introduction to the Biochemistry of Hormones and their Mechanism of Actions

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## Objectives:

To study the nature, types, general mechanism of action of hormones.

To learn about the chemistry, synthesis, metabolic role of various hormones.

# Contents

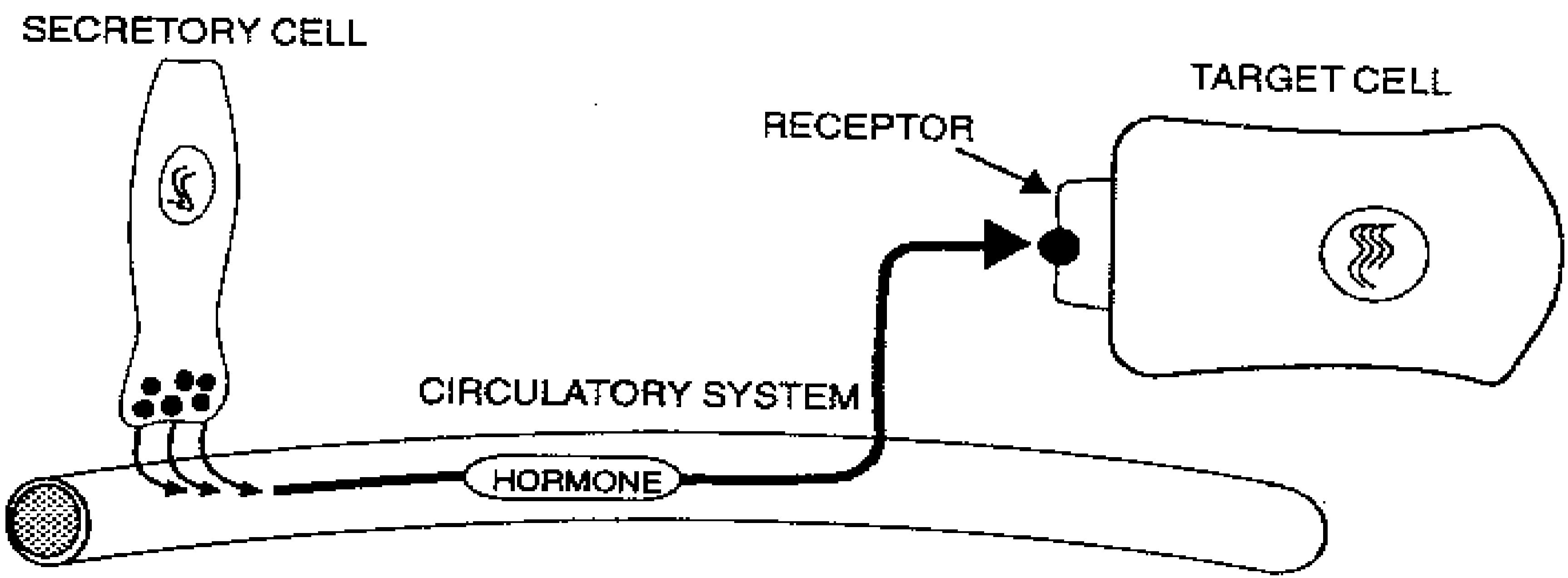
# Introduction

Homeostasis, the tendency to maintain stability, is essential to survival. It is achieved by a system of control mechanisms. Endocrine control is achieved by biochemical regulators. Some of these are **hormones**, they are released from specialized **glands** into the blood to influence the activity of cells and tissues at distance sites.

## Introduction

A **hormone** is a chemical substance released by a cell or a gland in one part of the body that sends out messages that affect cells in other parts of the organism. Only a little amount of hormone is required to alter cell metabolism, it is a **chemical messenger** that transports a signal from one cell to another.

The endocrine system consists of a group of **endocrine glands** that secrete **hormones** into the bloodstream. These hormones, which travel to all parts of the body, exert specific catalytic effects on target tissues.



**General functions of hormones**

- Stimulation or inhibition of growth mood swings
- Induction or suppression of apoptosis (programmed cell death)
- Activation or inhibition of the immune system
- Regulation of metabolism
- Preparation of the body for mating, fighting, fleeing, and other activity
- Preparation of the body for a new phase of life, such as puberty, parenting, and menopause control of the reproductive cycle

## Classification of hormones:

Hormones can be classified according to chemical natures (***molecular structure***), site of action, and solubility properties.

## 1- Chemical natures (***molecular structure):***

### ***A- Peptides and proteins:***

Peptide and protein hormones are products of translation. Lipid insoluble, large, complex, structure can differ among species due to amino acid substitutions.

Most peptide hormones circulate unbound to other proteins. In general, the half-life of circulating peptide hormones is only a few minutes.

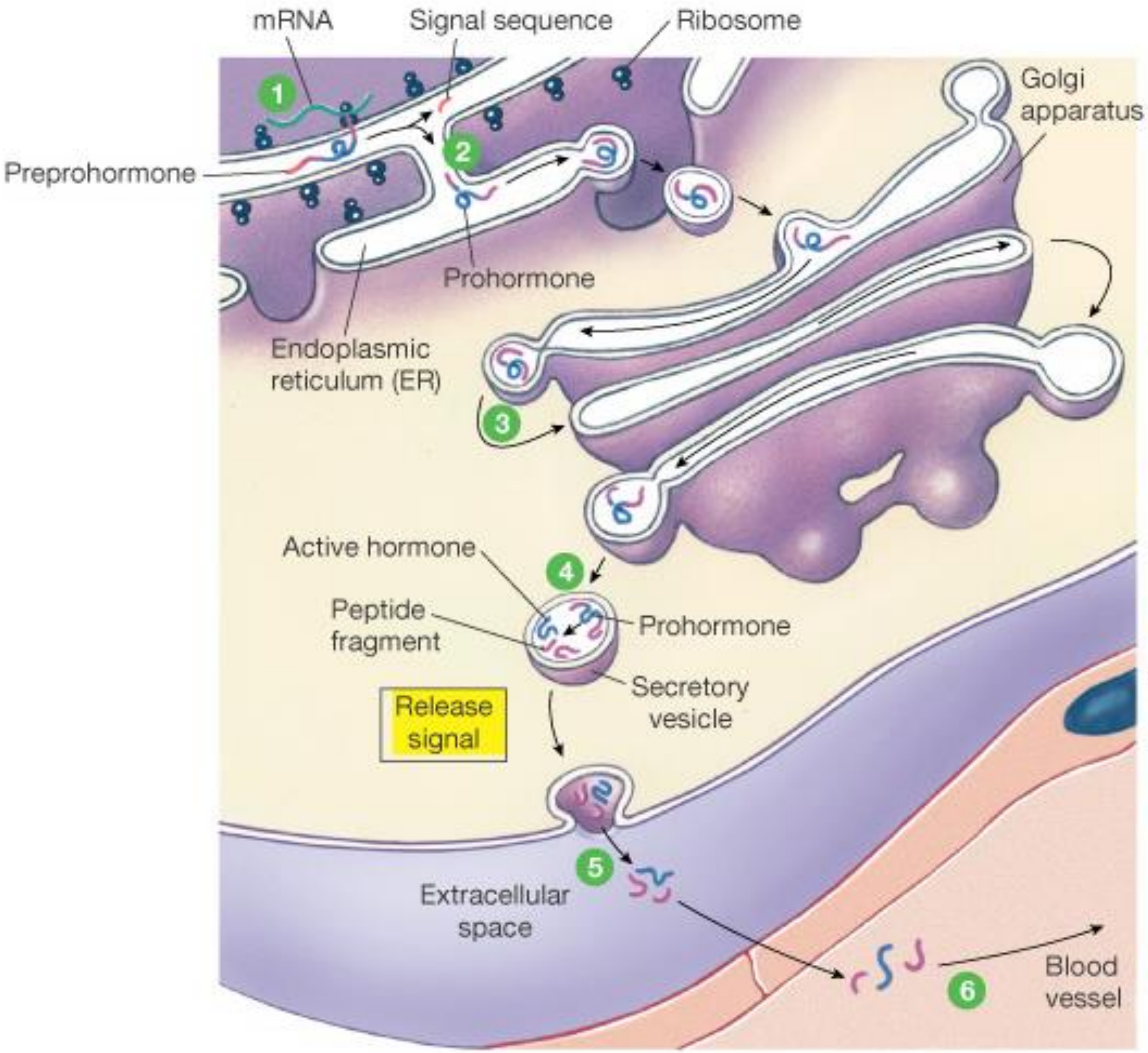
## The anterior pituitary secretes:

Luteinizing hormone and follicle stimulating hormone, those act on the gonads.

## The posterior pituitary gland secretes:

Antidiuretic hormone, also called vasopressin, and Oxytocin.

# Protein and Polypeptide Hormones: Synthesis and Release




1. Messenger RNA on the ribosomes of the ER binds amino acids into a peptide chain called a **preprohormone**. The chain is directed into the ER lumen by a **signal sequence** of amino acids.
2. Enzymes in the ER chop off the signal sequence, creating an inactive **prohormone.**
3. The prohormone passes from the ER through the Golgi apparatus.
4. Secretory vesicles containing enzymes and prohormone bud off the Golgi. The enzymes chop the prohormone into one or more active peptides plus additional peptide fragments.
5. The secretory vesicle releases its contents by exocytosis into the extracellular space.
6. The hormone moves into the circulation for transport to its target.

Figure 7-3: Peptide hormone synthesis, packaging, and release

***B-Amines-*** Small molecules, lipid insoluble derived from amino acids.

There are two groups of hormones derived from the amino acid tyrosine:

**Thyroid hormones** are basically a "double" tyrosine with the critical incorporation of 3 or 4 iodine atoms.

**Catecholamines** include epinephrine and norepinephrine, which are used as both hormones and neurotransmitters.

# Amine Hormone Structure

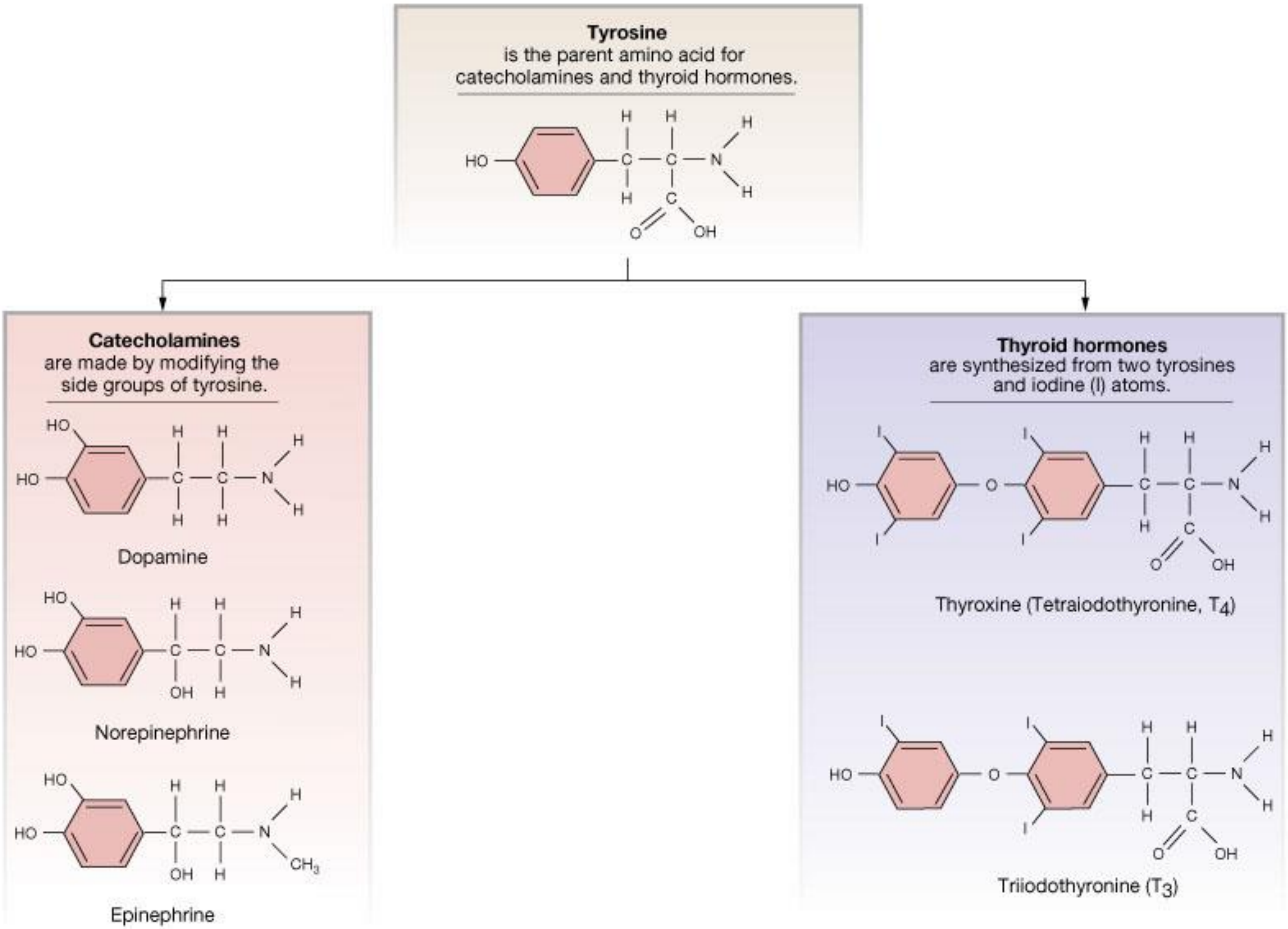



Figure 7-8: Tyrosine-derived amine hormones

***C-Steroids*** - cyclic hydrocarbons, lipid soluble **more specifically, derivatives of cholesterol**

Examples include ;

Sex steroids such as testosterone and Adrenal steroids such as cortisol. Corticosteroids, mineralocorticoides, androgens, oestrogens, progesterone.

# Steroid Hormones: Structure

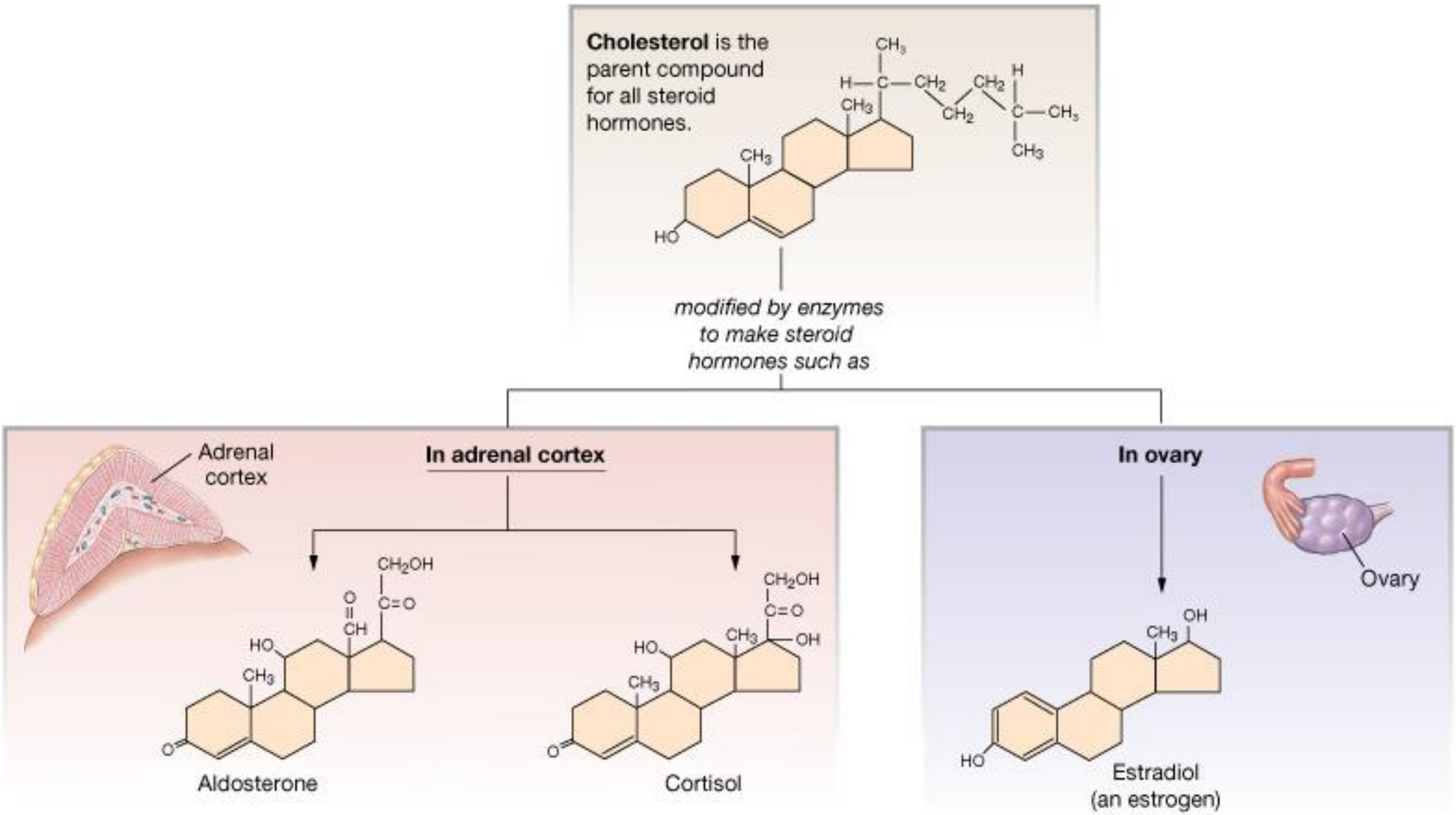



Figure 7-6: Steroid hormones are derived from cholesterol

## *2- Site of action.*

Secretions can be categorized by the site of action relative to the site of secretion.

***Autocrine*** secretion - substance released by cell that affects the secreting cell **itself** (e.g. norepinephrine is released by a neurosecretory cell in the adrenal medulla, and norepinephrine itself inhibits further release by that cell - this is also an example of direct negative feedback).

***Paracrine*** secretion - substance released by cell that affects **neighboring** cells. Not released into bloodstream (e.g. histamine released at site of injury to constrict blood vessel walls and stop bleeding).

# Paracrine and Autocrine Hormones

- Local communication
- Signal chemicals diffuse to target
  - Autocrine–receptor on same cell
  - Paracrine–neighboring cells

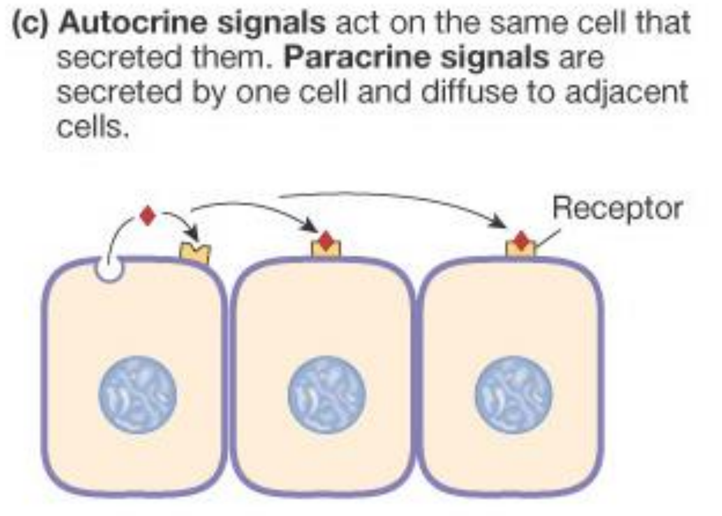



Figure 6-1c: Direct and local cell-to-cell communication

## *Endocrine*

Secretion - substance released by cell into bloodstream that affects distant cells. (e.g. testosterone is secreted by Leydig cells in testis, makes hair grow on the back).

# Long Distance Communication: Endocrine Hormones

- Signal Chemicals
- Made in endocrine cells
- Transported via blood
- Receptors on target cells

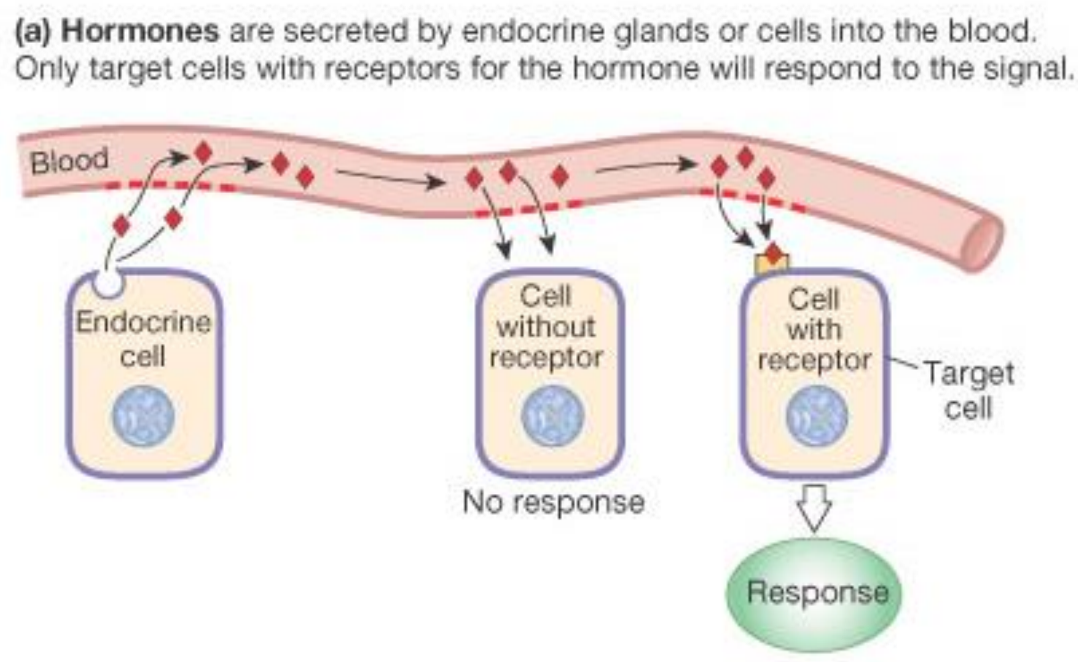
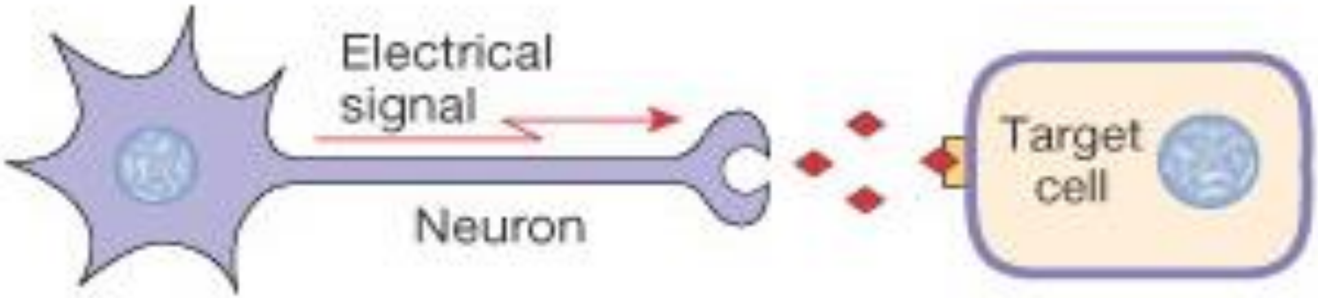
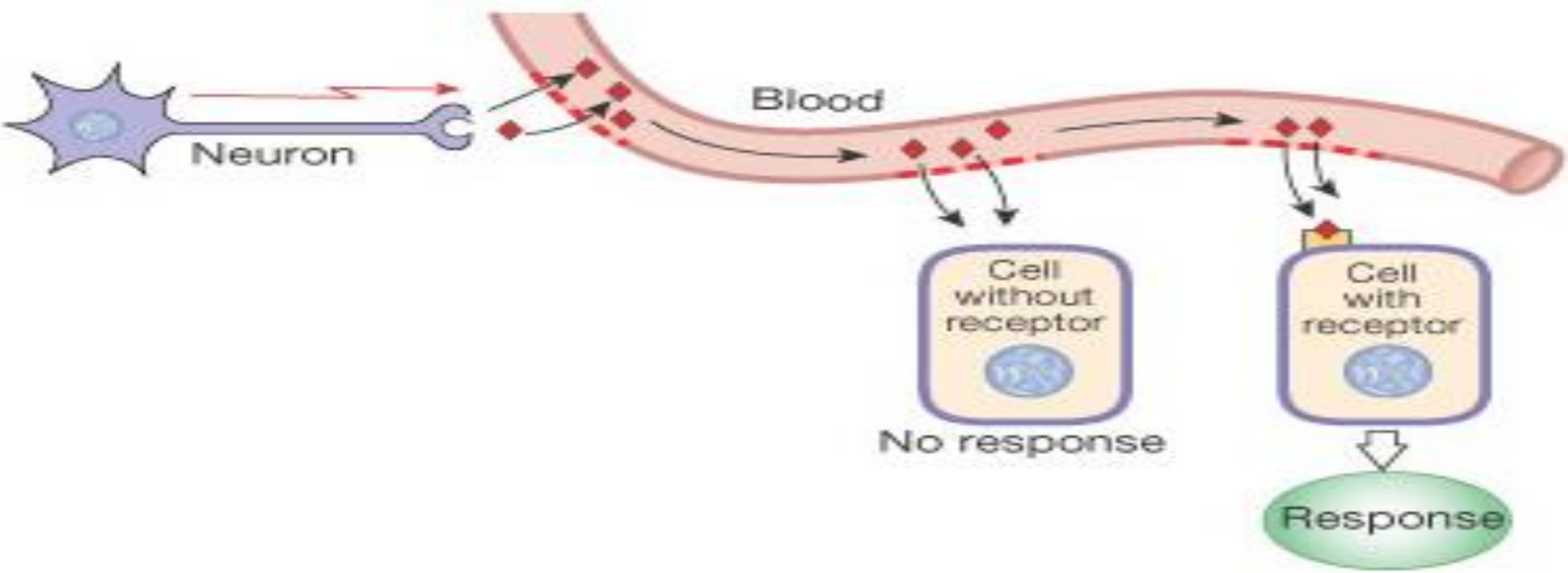



Figure 6-2a: Long distance cell-to-cell communication

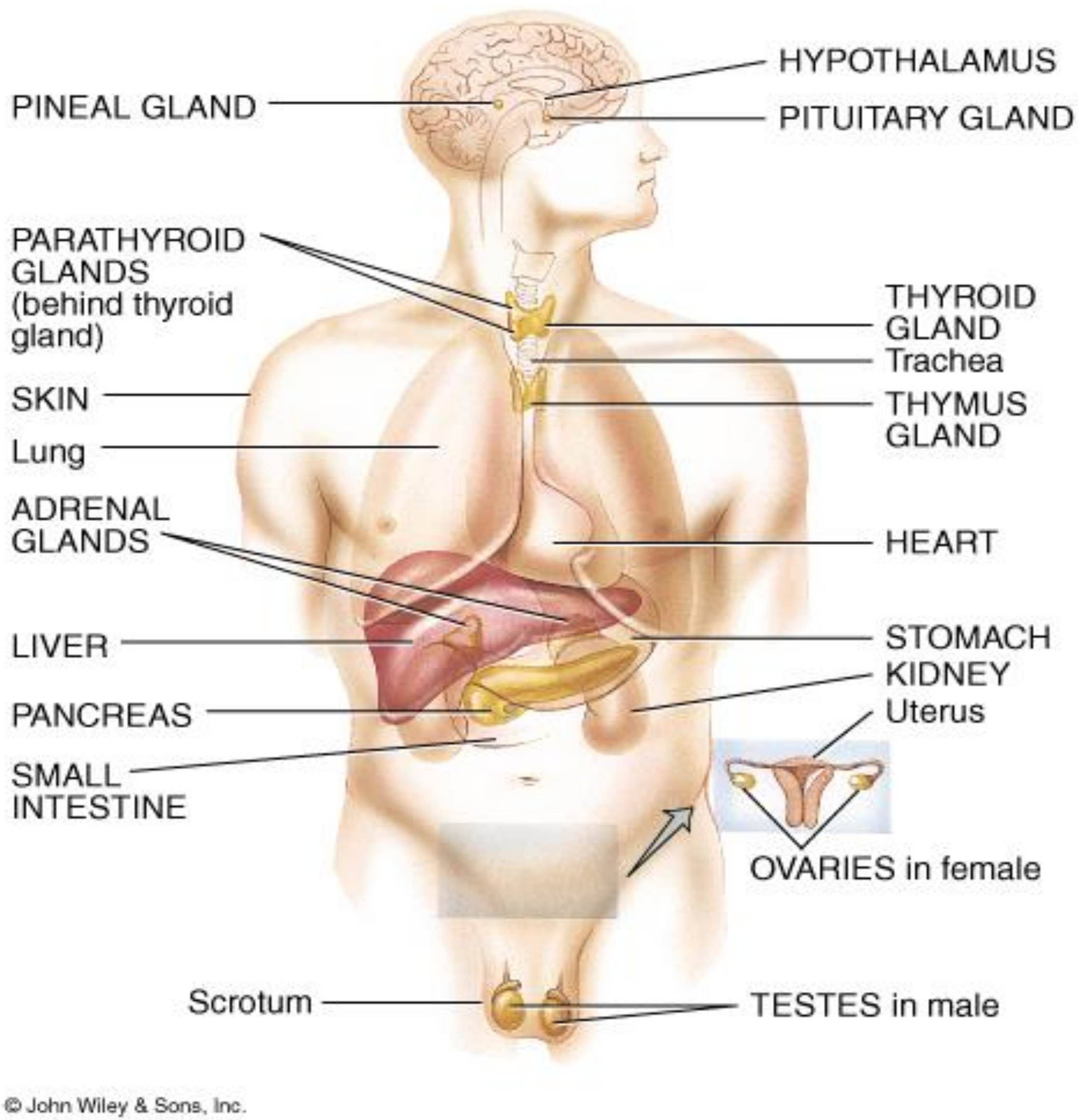
**(b) Neurotransmitters** are chemicals secreted by neurons that diffuse across a small gap to the target cell. Neurons use electrical signals as well.




**(c) Neurohormones** are chemicals released by neurons into the blood for action at distant targets.



# Endocrine System




FUNCTIONS OF HORMONES

1. Help regulate:
   - chemical composition and volume of internal environment (extracellular fluid)
   - metabolism and energy balance
   - biological clock (circadian rhythms)
   - contraction of smooth and cardiac muscle fibers
   - glandular secretions
   - some immune system activities.
2. Control growth and development.
3. Regulate operation of reproductive systems.

## 3- classification according solubility properties

### A- Lipophilic (lipid soluble hormones )

After secretion, these hormones associate with plasma transport or carrier proteins. The free hormone, which is the biologically active form, readily traverses the lipophilic plasma membrane of all cells and intracellular receptor proteins in either the cytosol or nucleus of target cells. The ligand-receptor complex is assumed to be the intracellular messenger in this group.

1- Steroid hormones (eg. Cortisol, testosterone.)

2- Thyroid hormones (eg. T3, and T4).

## B- Water-soluble hormones

That bind to the plasma membrane of the target cell. Hormones that bind to the surfaces of cells communicate with intracellular metabolic processes through intermediary molecules called **second messengers** (the hormone itself is the first messenger), which are generated as a consequence of the ligand-receptor interaction, include;

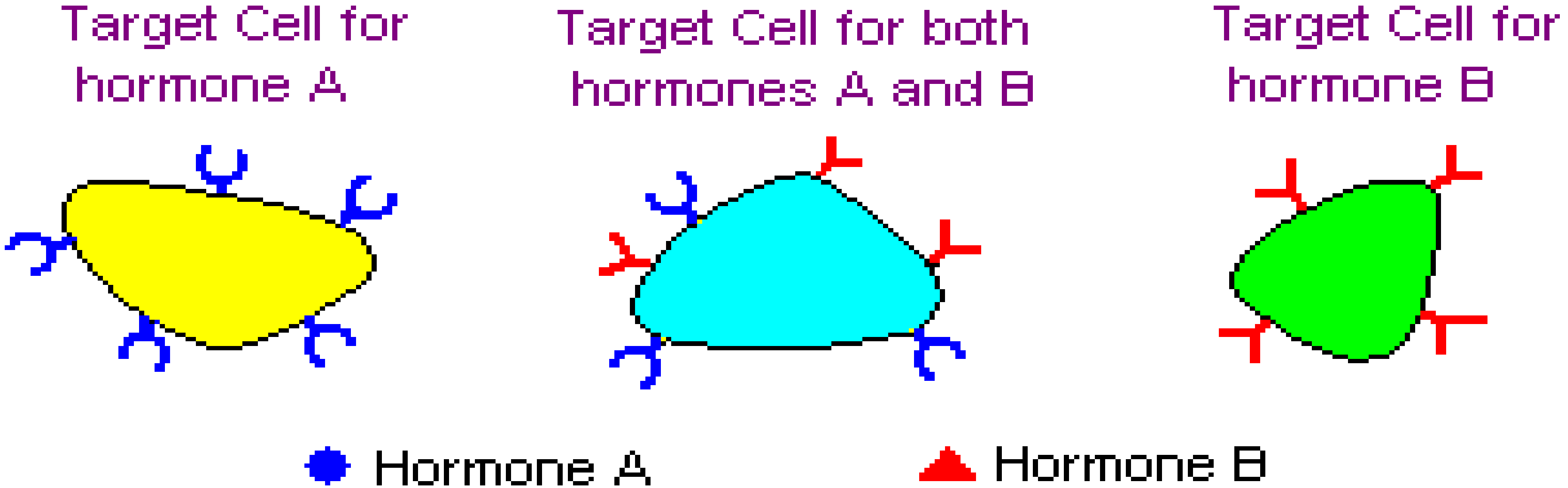
1- Catecholamin hormones (eg. Epinephrine)

2- Peptide hormones (eg. Thyrotropin-releasing hormone {TRH})

3- Protein hormones ( eg. Insulin).

# Hormone receptors and target Cells

A given hormone usually affects only a limited number of cells, which are called target cells. A target cell responds to a hormone because it bears receptors for the hormone.



A hormone receptor is a molecule that can bind to a specific hormone. are found either exposed on the surface of the cell or within the cell, depending on the type of hormones.

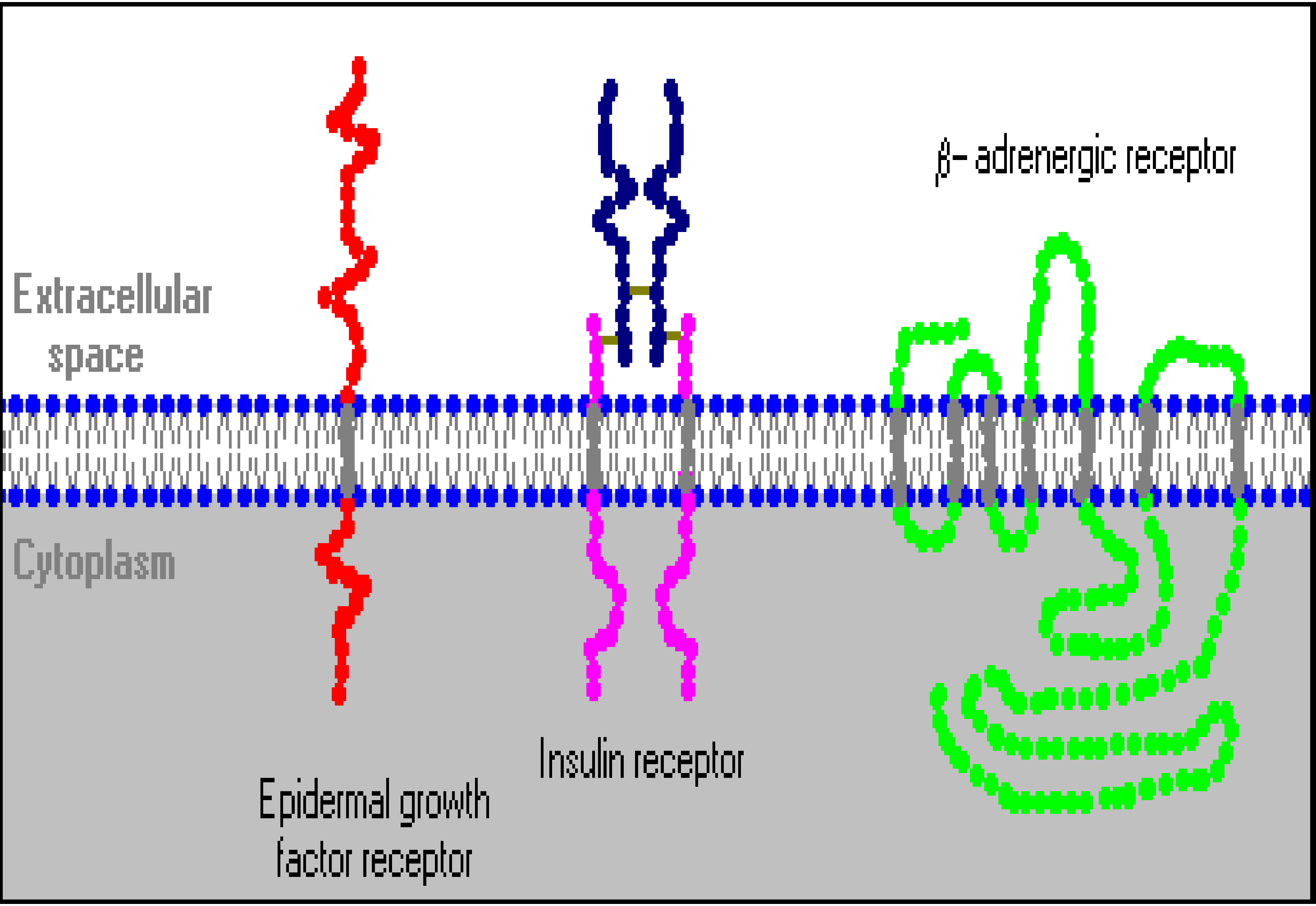
Upon hormone binding, the receptor can initiate multiple signaling pathways which ultimately lead to changes in the behavior of the target cells.

# General mechanisms of hormone action

## 1- Hormones that bind to cell membrane receptors (water soluble hormones)

### A- Hormones that activate tyrosine kinases

Insulin binds to a receptor on the cell surface, causing the β subunits of the receptor to phosphorylate themselves on tyrosine residues located on the inner surface. The phosphorylated receptor acts as kinase, phosphorylating an intracellur protein known as insulin receptor substrate-1 (IRS-1), phosphorylated IRS-1 then activated other signal transduction proteins, initiating a sequence of events that ultimately produce the intracellular effects of insulin.



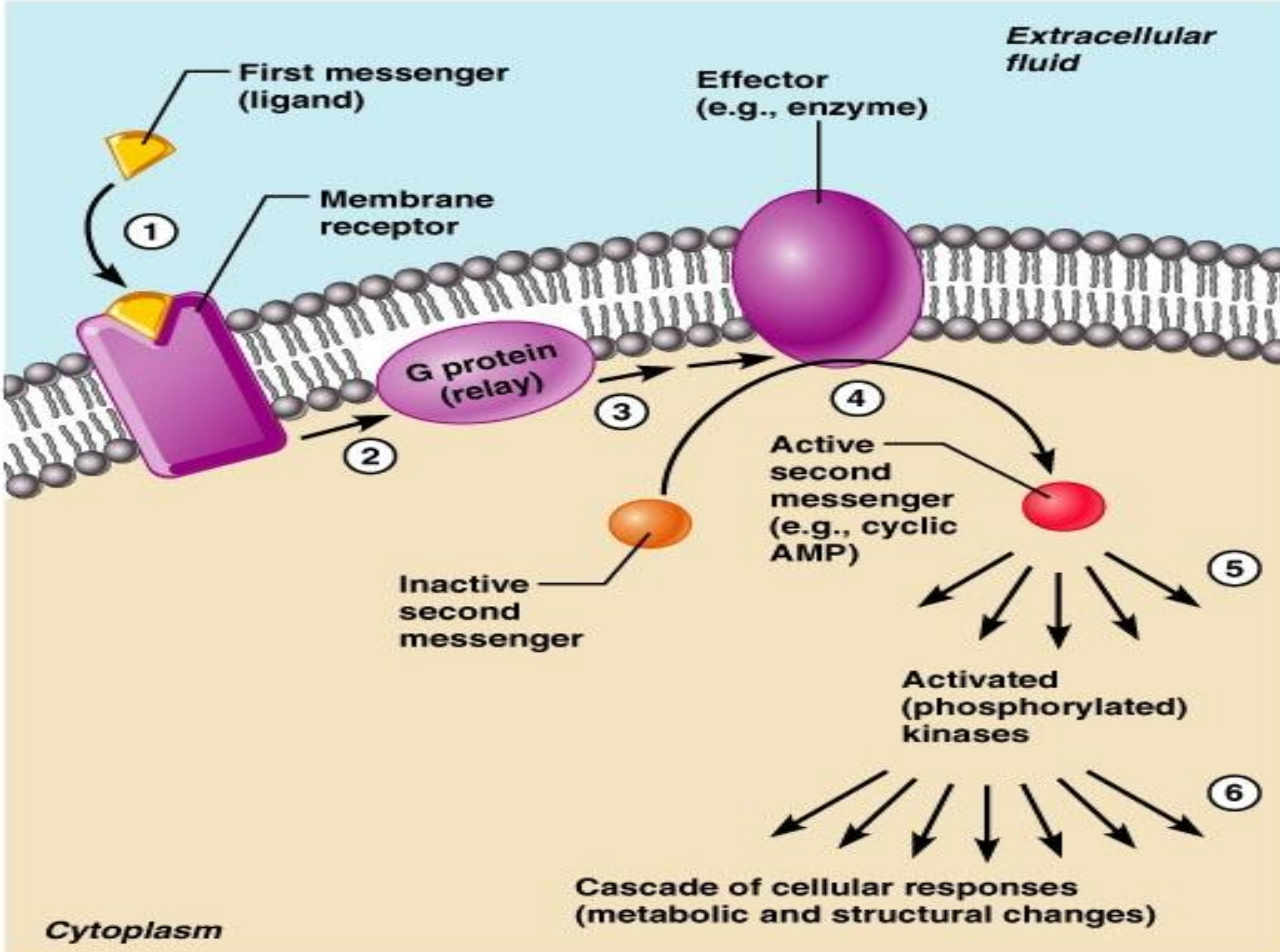
β- adrenergic receptor
Extracellular space
Cytoplasm
Insulin receptor
Epidermal growth factor receptor

## B- hormones that act through cyclic nucleotides

Epinephrine and certain polypeptide hormones, such as glucagon, bind to receptors on the external surface of the cell membrane, these hormone receptor complexes interact with G protein, and activate adenylate cyclase, which converts ATP to cAMP.

cAMP activates protein kinase A, which subsequently phosphorylates certain intracellular proteins, altering their activity.

Some of hormone-receptor complexes lower cAMP levels, either by inhibiting adenylate cyclase or by activating the phosphodiesterase that cleaves cAMP to AMP.


Extracellular fluid
First messenger (ligand)
Effector (e.g., enzyme)
Membrane receptor
1
G protein (relay)
2
3
4
Active second messenger (e.g., cyclic AMP)
Inactive second messenger
5
Activated (phosphorylated) kinases
6
Cascade of cellular responses (metabolic and structural changes)
Cytoplasm

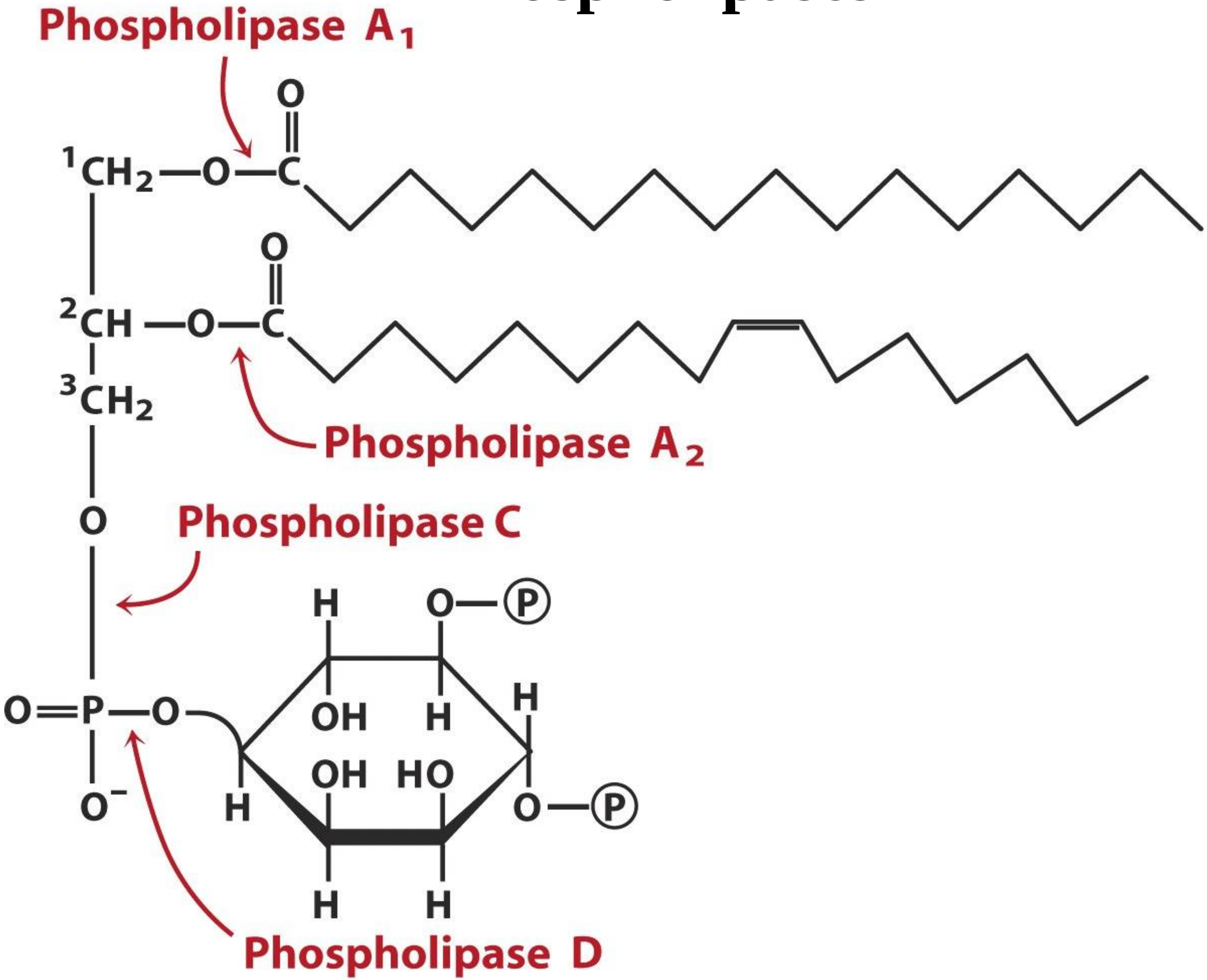
## C- hormones that act through calcium and phosphatidyl inositol bisphosphate (PIP2) system.

Some hormones (eg. Thyrotropin-releasing hormone)[TRH] , and oxytocin [OT] interact with G proteins to alter the amount and distribution of Ca ions within the cell and activate protein kinase C.

Hormone-G protein complexes open calcium channels within the cell membrane, allowing extracellular calcium to move into the cell.

Some complexes activate phospholipase C, which cleaves phosphatidyl inositol diphosphate (PIP2) in the cell membrane to produce to messengers, diacylglycerol (DAG), and inositol triphosphate (IP3).

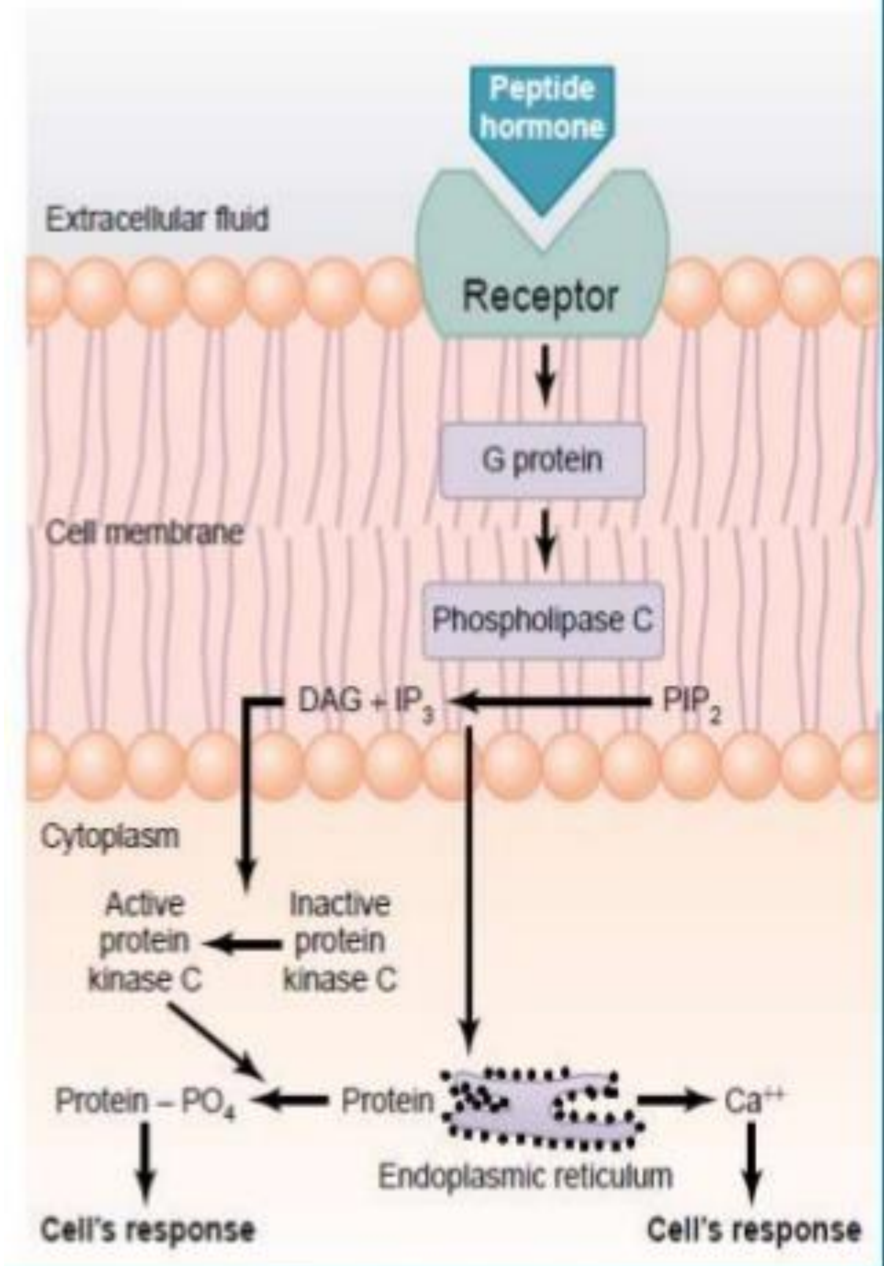
# Phospholipases



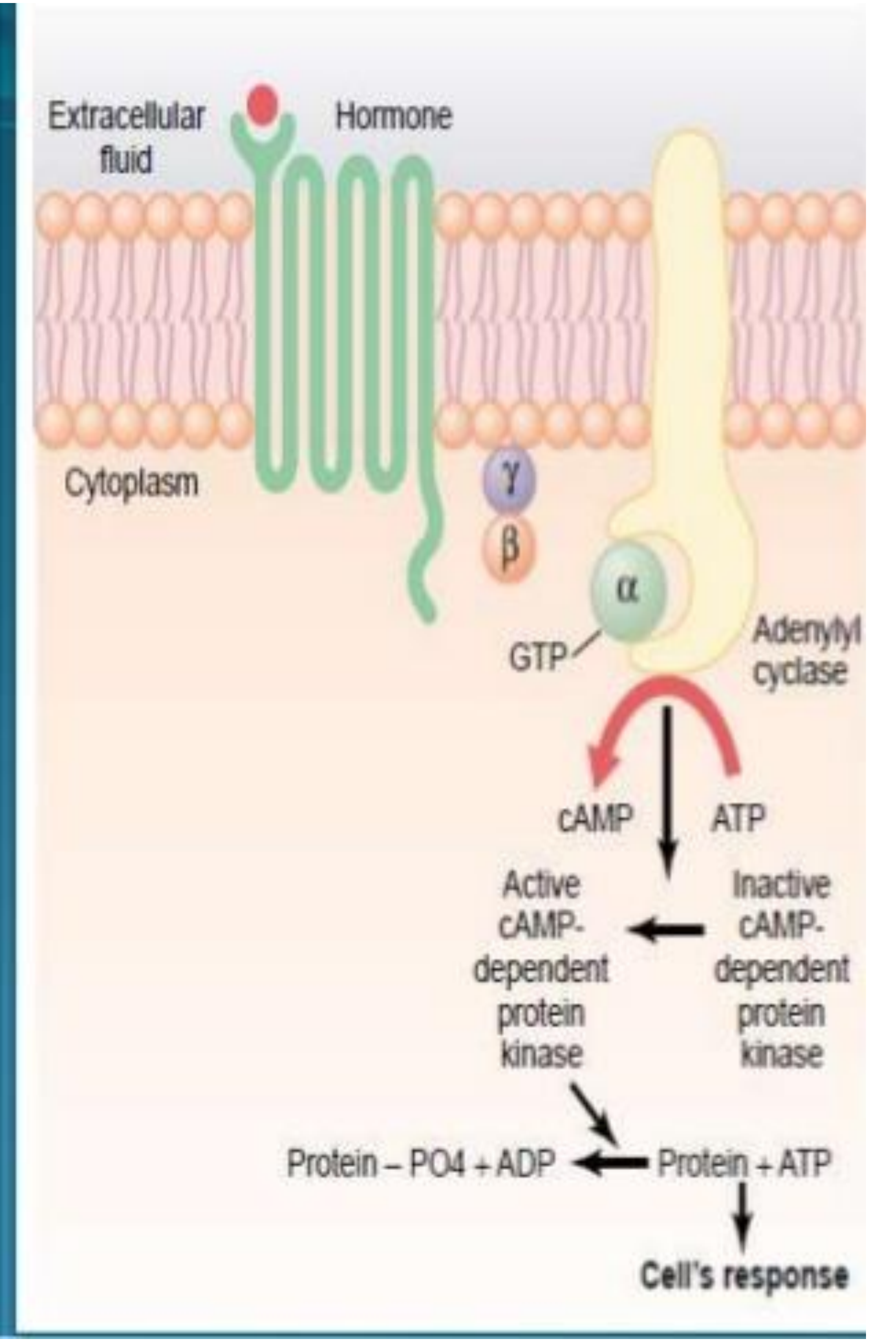
DAG activates protein kinase C, which phosphorylates certain proteins, altering their activity.

IP3 causes calcium ions to be released from intracellular stores, such as those in the endoplasmic reticulum.

Calcium ions, either directly or complexed with Calmodulin, interacts with proteins, altering their activity.



Peptide hormone
Extracellular fluid
Receptor
G protein
Cell membrane
Phospholipase C
DAG + $IP_3$
$PIP_2$
Cytoplasm
Active protein kinase C
Inactive protein kinase C
Protein – $PO_4$
Protein
$Ca^{++}$
Endoplasmic reticulum
Cell's response
Cell's response



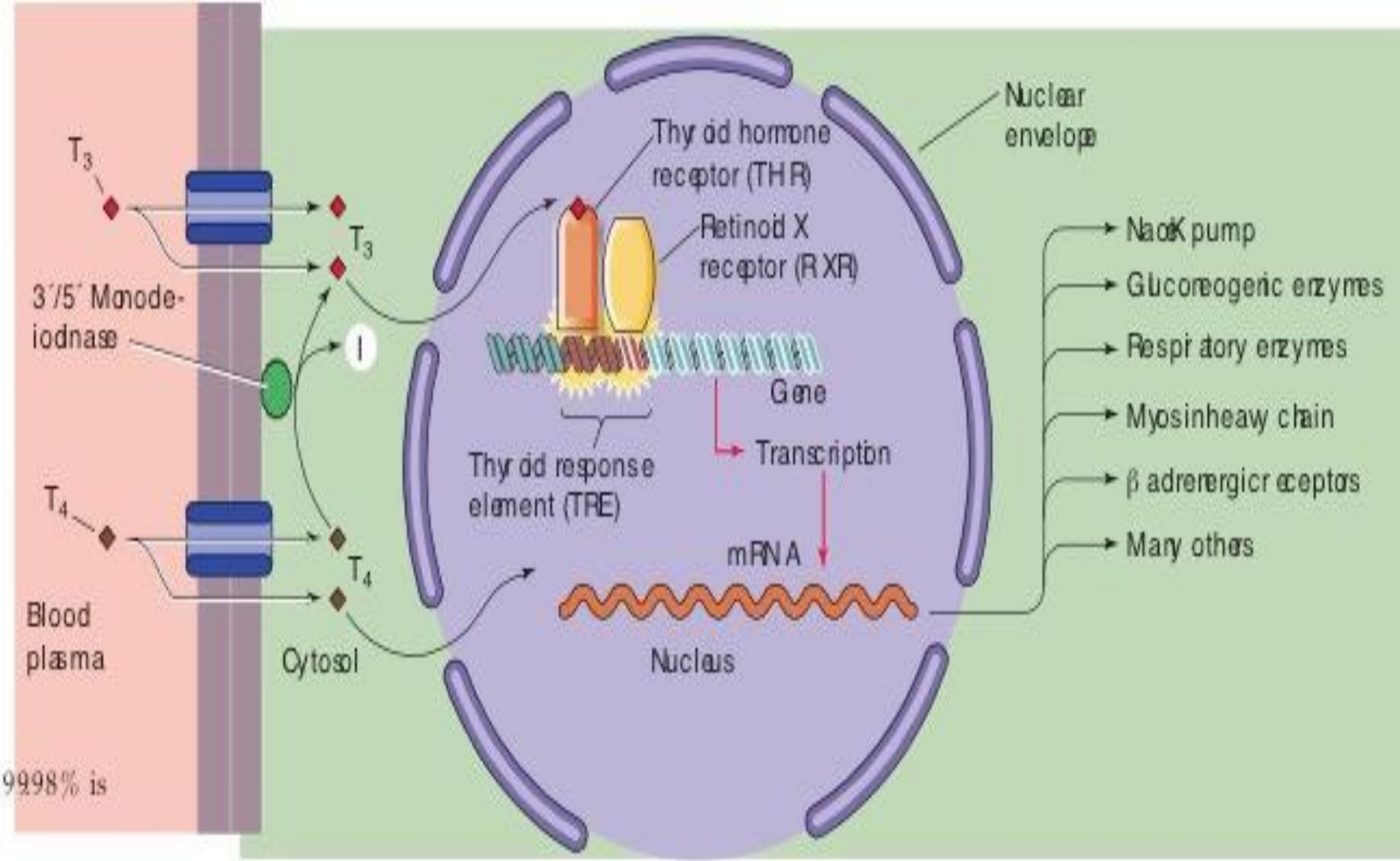
Extracellular fluid
Hormone
Cytoplasm
γ
β
α
GTP
Adenylyl cyclase
cAMP
ATP
Active cAMP-dependent protein kinase
Inactive cAMP-dependent protein kinase
Protein – PO4 + ADP
Protein + ATP
Cell's response

## 2-Hormones that bind to intracellular receptors and activate genes. ( Lipid soluble hormones).

- Steroid and thyroid hormones, 1,25-dihydroxycholecalceferol (1,25-DHC), and retinoic acid cross the cell membrane and bind to intracellular receptors.

- Intracellular receptors

The hormone transport to the intracellular directly, and in cytoplasm or nucleus bind with a receptor, and bind with DNA that stimulate or inhibit the synthesis of messenger RNA (mRNA). Translation of this mRNA produces proteins that are responsible for the physiologic effects of the hormone.



$T_3$
$T_3$
3´/5´ Monode-iodinase
I
$T_4$
$T_4$
Blood plasma
Cytosol
99.98% is
Nuclear envelope
Thyroid hormone receptor (THR)
Retinoid X receptor (RXR)
Gene
Thyroid response element (TRE)
Transcription
mRNA
Nucleus
Na/K pump
Gluconeogenic enzymes
Respiratory enzymes
Myosin heavy chain
β adrenergic receptors
Many others

# Receptor locations

- Cytosolic or Nuclear
  - Lipophilic ligand enters cell
  - Often activates gene
  - Slower response
- Cell membrane
  - Lipophobic ligand can't enter cell
  - Outer surface receptor
  - Fast response

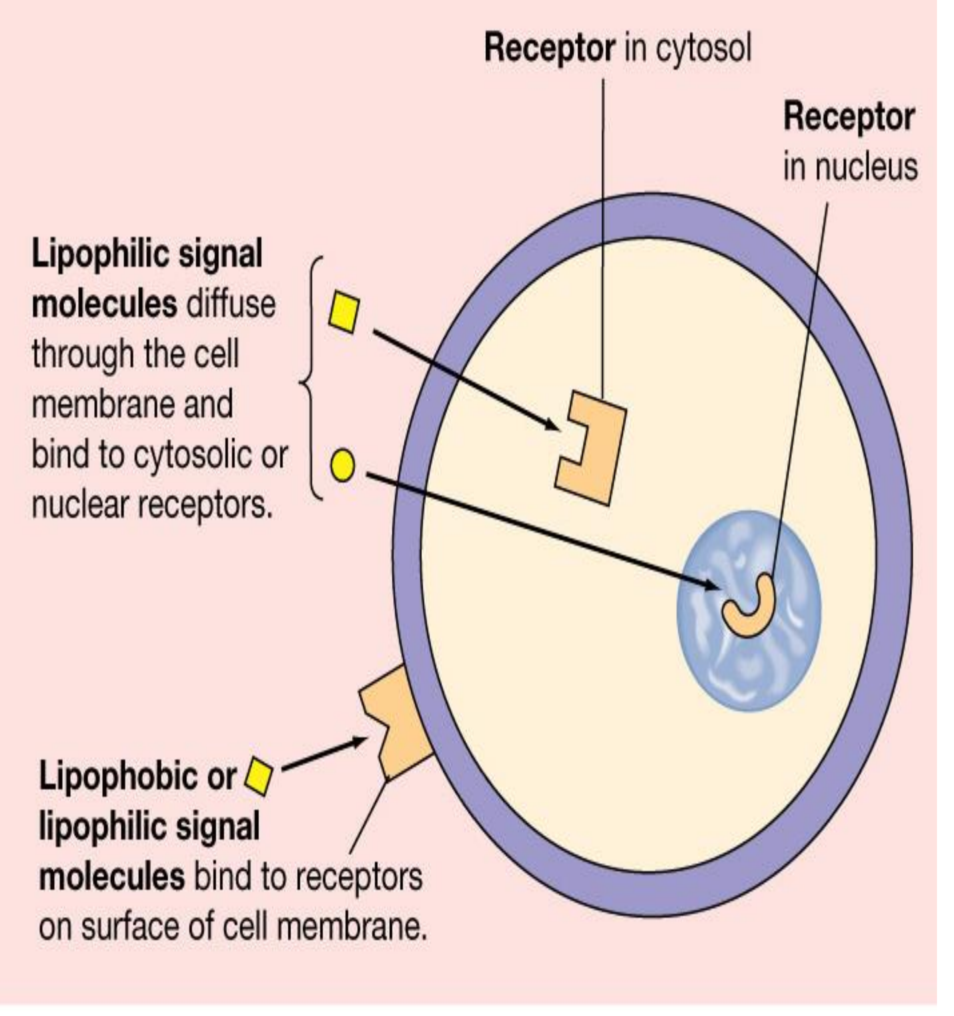



Figure 6-4: Target cell receptors

## Regulation of hormone levels

### 1- Regulation of hormone synthesis and secretion:

The release of hormones is stimulated by changes in the environment or physiologic state or by stimulatory hormone from another tissue that acts on the cells that release the hormone for example:

- A decrease in blood pressure initiates a sequence of events that ultimately causes the adrenal gland to release aldosterone.

- In response to stress, the hypothalamus releases corticopotropin- releasing hormone (CRH), which stimulates the anterior pitutary to release adrenocorticotropic hormone (ACTH), ACTH stimulates the adrenal gland to release cortisol.

- The physiological effect of the hormone or the hormone itself causes a decrease in the signal that initially promoted the synthesis and release of the hormone for example;

- ❑ Aldosterone causes an increase resorption from the kidney tubule of sodium and consequently, of water, increasing blood pressure.
- ❑ Cortisol feeds back on the hypothalamus and the anterior pituitary, inhibiting the release of CRH and ACTH.

# Hormone inactivation

After hormones exert their physiologic effects, they are inactivated and exerted or degraded.

- Some of hormones are converted to compounds that are no longer active and may be readily excreted from the body.

**For example,** cortisol, a steroid hormone, is reduced and conjugated with glucuronide or sulfate and excreted in the urine and the feces.

- Some hormones, particularly the polypeptides, are taken up by cells via the process of endocytosis and subsequently degraded by lysosomal enzymes.
- The receptor, which is internalized along with the hormone, can be degraded by lysosomal proteases.

## **Feedback Control of Hormone Production (*Modulation of an endocrine response)***

Feedback circuits are at the root of most control mechanisms in physiology, and are particularly prominent (obvious) in the endocrine system. Instances of positive feedback certainly occur, but negative feedback is much more common.

Feedback loops are used extensively to regulate secretion of hormones in the hypothalamic-pituitary axis.

Feedback is usually ***negative***, so that endocrine response is self-limiting; secretion modulates itself and does not 'run away'.

Feedback is sometimes ***positive***, when a quick, large response is necessary. When a system shows positive feedback, it will run away (like a microphone held near an amplifier) unless something changes to stop the positive feedback.

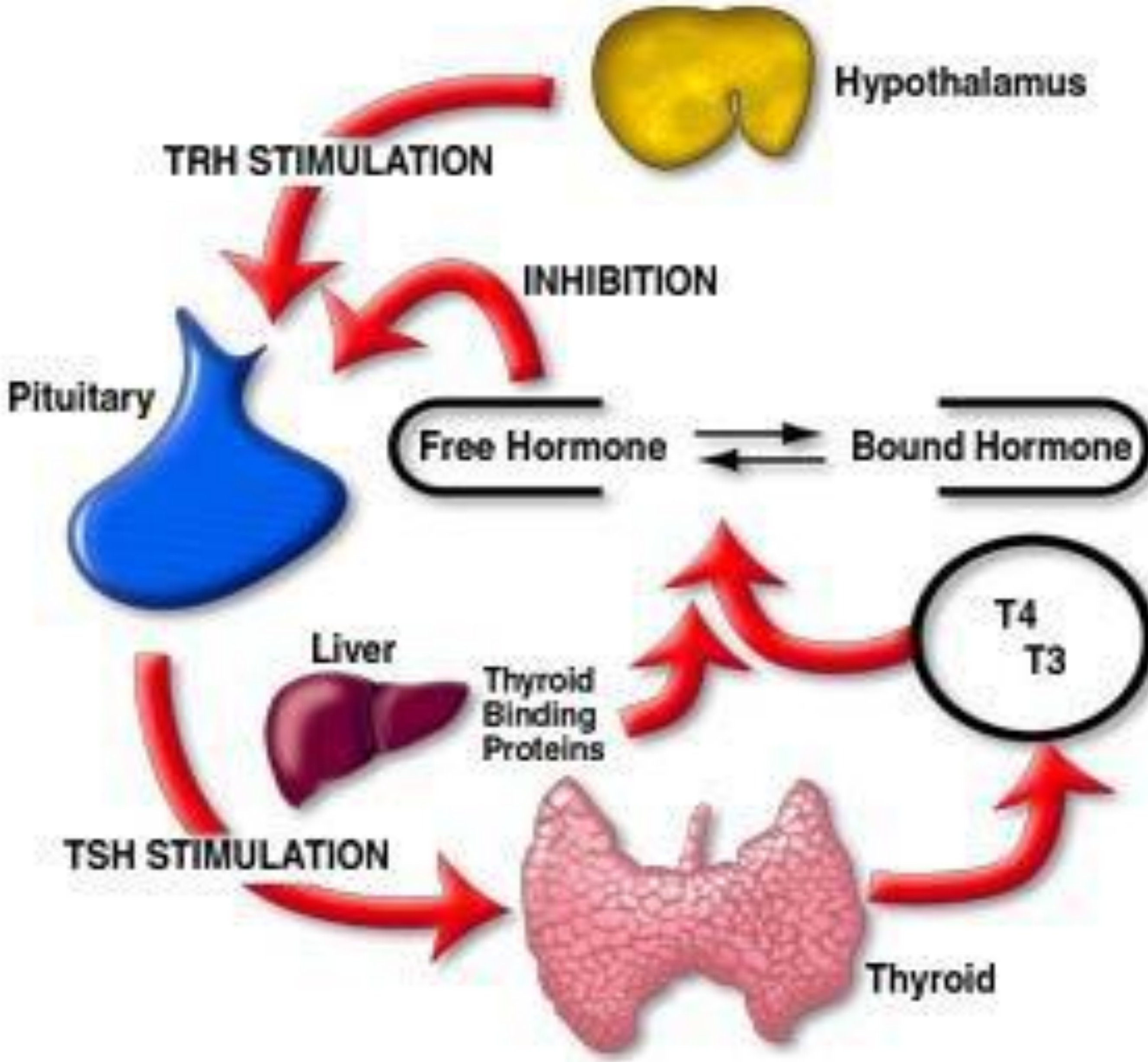
An important example of a negative feedback loop is seen in control of thyroid hormone secretion. The thyroid hormones thyroxine and triiodothyronine ("T4 and T3") are synthesized and secreted by thyroid glands and affect metabolism throughout the body. The basic mechanisms for control in this system are:

- Neurons in the hypothalamus secrete thyroid releasing hormone (TRH), which stimulates cells in the anterior pituitary to secrete thyroid-stimulating hormone (TSH).
- TSH binds to receptors on epithelial cells in the thyroid gland, stimulating synthesis and secretion of thyroid hormones, which affect probably all cells in the body.

When blood concentrations of thyroid hormones increase above a certain threshold, TRH-secreting neurons in the hypothalamus are inhibited and stop secreting TRH.

*This is an example of "negative feedback".*

Inhibition of TRH secretion leads to shut-off of TSH secretion, which leads to shut-off of thyroid hormone secretion. As thyroid hormone levels decay below the threshold, negative feedback is relieved, TRH secretion starts again, leading to TSH secretion...


Hypothalamus
TRH STIMULATION
INHIBITION
Pituitary
Free Hormone
Bound Hormone
T4
T3
Liver
Thyroid
Binding
Proteins
TSH STIMULATION
Thyroid