HORMONE: MECHANISM & ACTION

By

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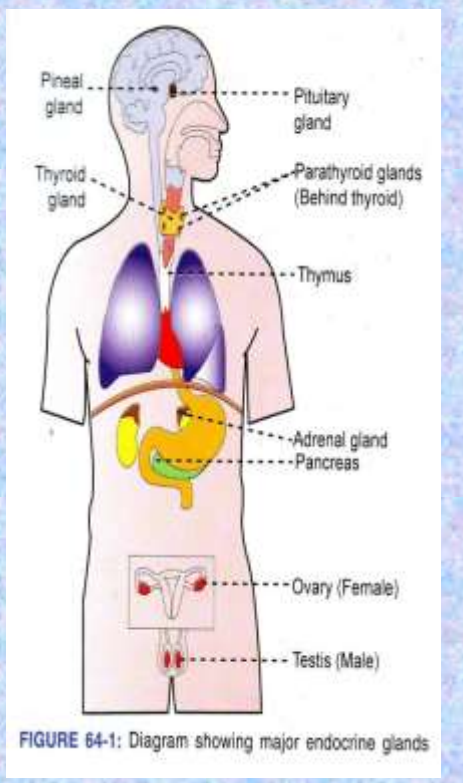


FIGURE 64-1: Diagram showing major endocrine glands

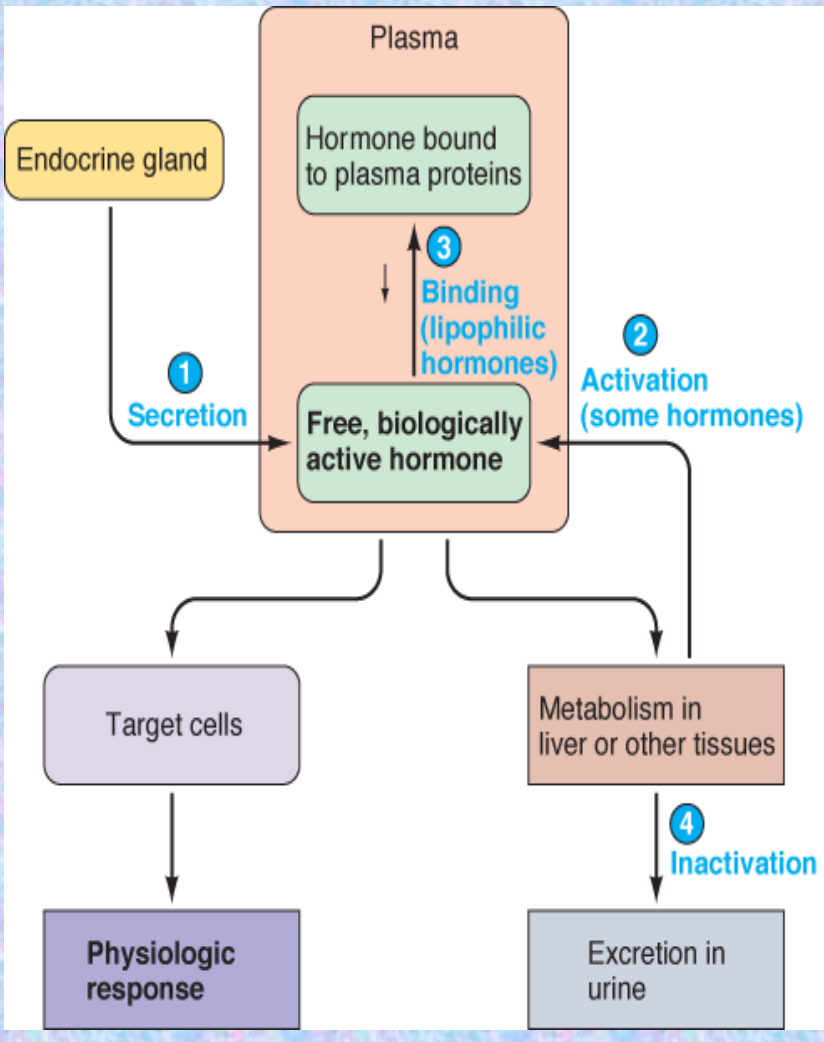
WHAT ARE HORMONES?

- Natural organic substances, that regulate growth, metabolism and other functions of an organism
- They are simply biochemical messengers
- They can be classified according to the chemical composition, organs where they work e.g reproductive hormones in the reproductive organs, and if they either act on the same cell producing them i.e. autocrine or paracrine

GENERAL PRINCIPLES OF HORMONE ACTION

- **Trophic hormone:-** A hormone that has its primary function the regulation of hormone secretion by another endocrine gland
- **Synergism-**when different hormones work together and have a greater effect than individual hormone action
- **Permissiveness**-a small amount of one hormone allows a second hormone to have its full effect on a target cell; i.e. first hormone 'permits' the full action of the second hormone
- **Antagonism-**one hormone produces the opposite effect of the other
- The processes involve in both negative and positive feedback. For example, if A>B>C>D, increase in D causes inhibition of A i.e. negative feedback. If D decreases, A production is triggered, i.e. positive feedback.

ONSET OF HORMONE SECRETION AND ACTION



The plasma concentration of free, biologically active hormone, which can interact with its target cells to produce a physiologic response, depends on

1. the hormone's rate of secretion by the endocrine gland (for all hormones; the major factor)
2. its rate of metabolic activation (for a few hormones)
3. its extent of binding to plasma proteins (for lipophilic hormones)
4. its rate of metabolic inactivation and excretion (for all hormones)

GENERAL CHARACTERISTICS OF HORMONES

- Not secreted at a uniform rate
- Exert their effects in biocatalytic amounts
- Turnover is varied and usually rapid
- Exert multiple actions
- Exhibit high degree of specificity
- Different tissues may respond differently to a given hormone

MECHANISM OF HORMONE ACTION

The hormones fall into two general classes based on their solubility in water.

- **1. Hydrophilic Hormone:** The water soluble hormone. They are transported simply dissolved in blood
- **Examples**: the catecholamines (epinephrine and norepinephrine) and peptide/protein hormones.
- **2. Lipophilic Hormone:** They are poorly soluble in water. So they cannot be dissolved in watery blood. They bind to plasma protein and present in the blood in protein bound form. They are lipid soluble.
- **Examples:** The lipid soluble hormones include thyroid hormone, steroid hormones and Vitamin D3

Broad Classification (Structure)

Hydrophillic

Proteins, peptide hormones & catecholamines

Primarily act through second messenger system

Circulate mainly dissolved in the plasma

Lipophillic

Steroid and thyroid hormones

Activate genes on binding with receptors in the nucleus

Largely bound to plasma proteins

Signal Amplification Via 2nd Messenger Pathways

Initial signal is in the form of hormone which acts as ligand whose concentration is just one/per receptor. The hormonal response has got multiple steps, and each step multiplies the signal (cascading effect) that finally leading to million fold amplification, i.e. one hormone molecule mediating its effect through million of molecules. This process is known as signal amplification.

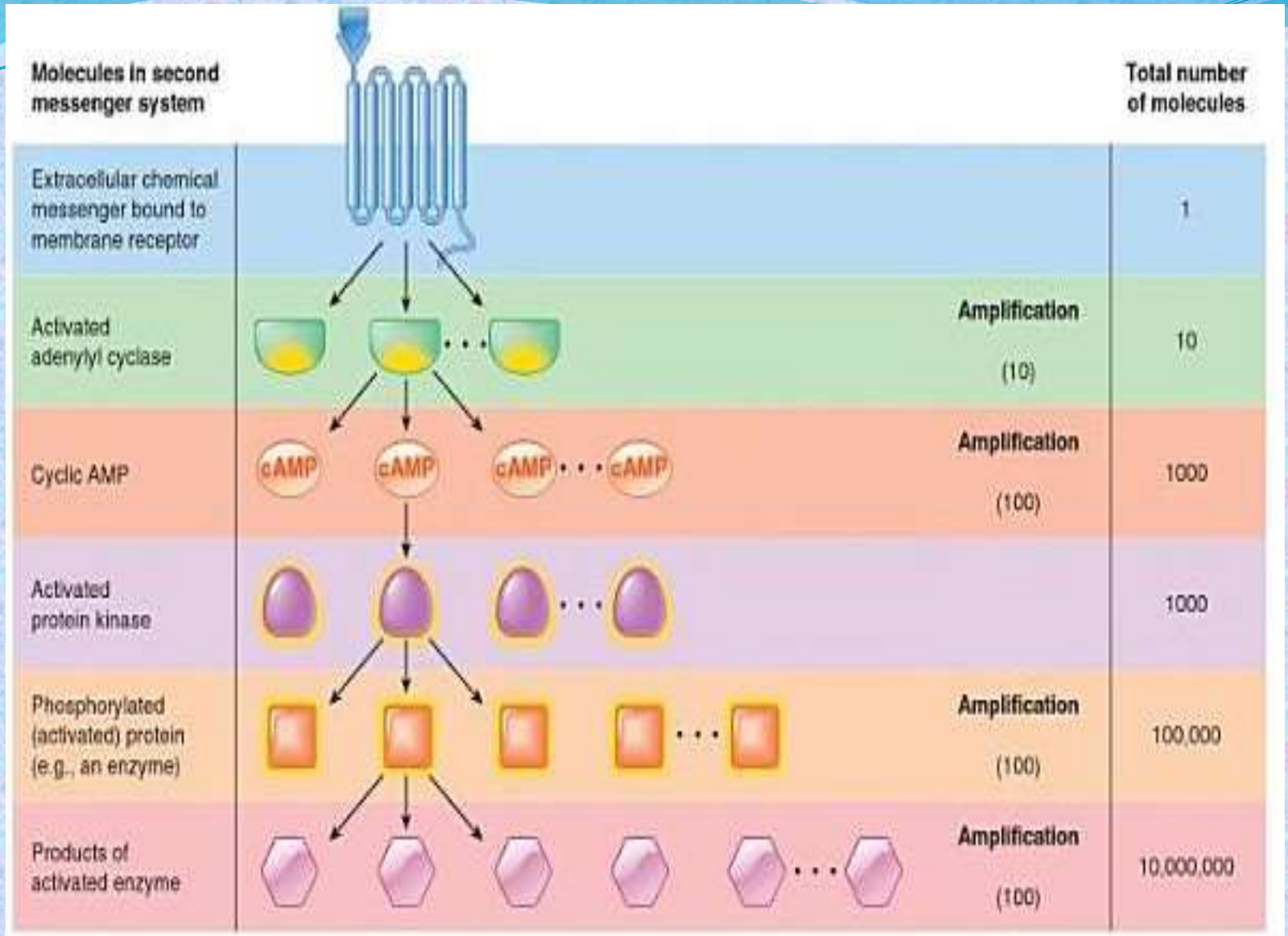
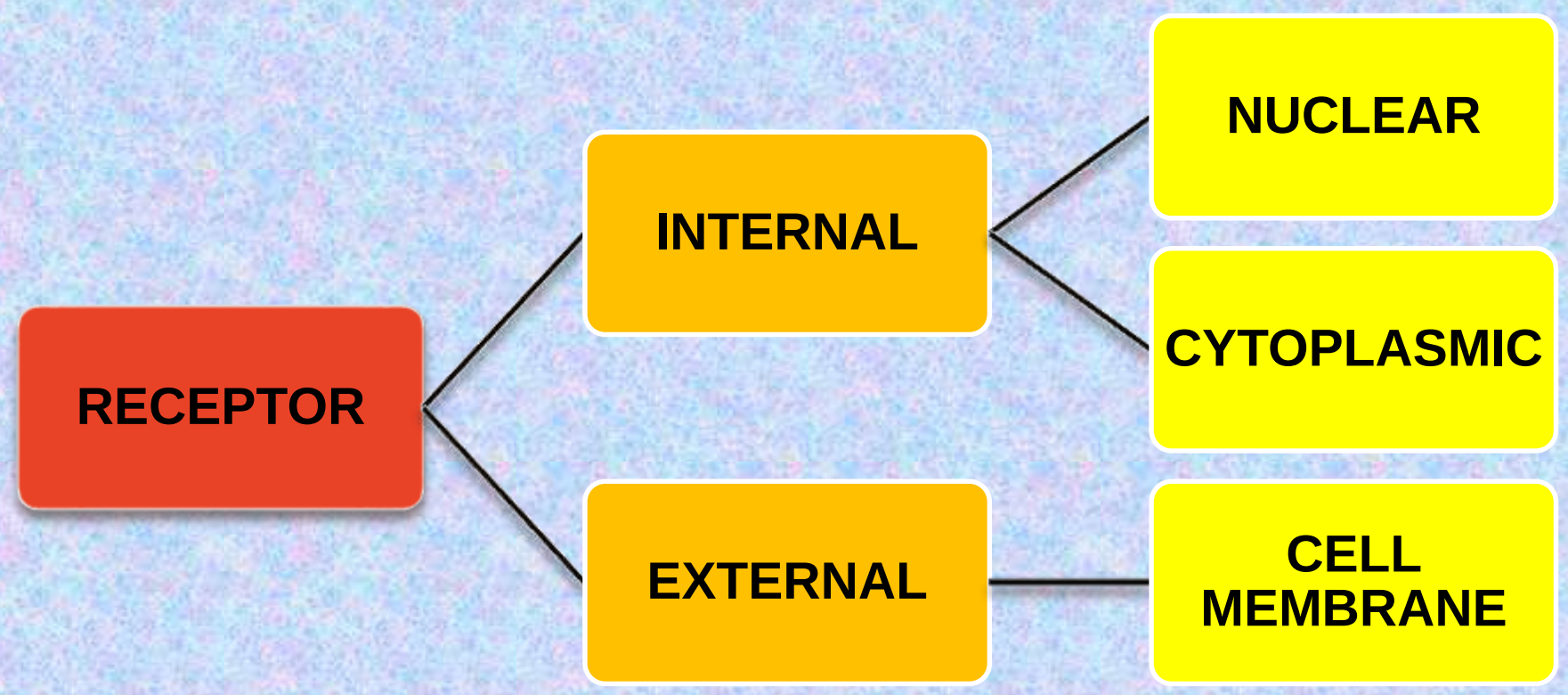


FIGURE 4-26 Amplification of the initial signal by a second-messenger pathway.

MODE OF HORMONE ACTION

- Generally hormones work in two ways
- ✓ 1-synthesis of new protein molecules
- ✓ 2- changing cell permeability
- Lipid-soluble hormones involves in 'MOBILE-RECEPTOR HYPOTHESIS' whereas water-soluble hormones involves in 'THE SECOND-MESSENGER MECHANISM'

TYPES OF RECEPTOR



MEMBRANE RECEPTOR

- Receptors present in or on the surface of the cell membrane.

Types

- **Ion channel-linked receptor**
- **G –protein couple receptor**
- **Enzyme –linked receptor**

- E.g., Proteins, peptides, & catecholamines

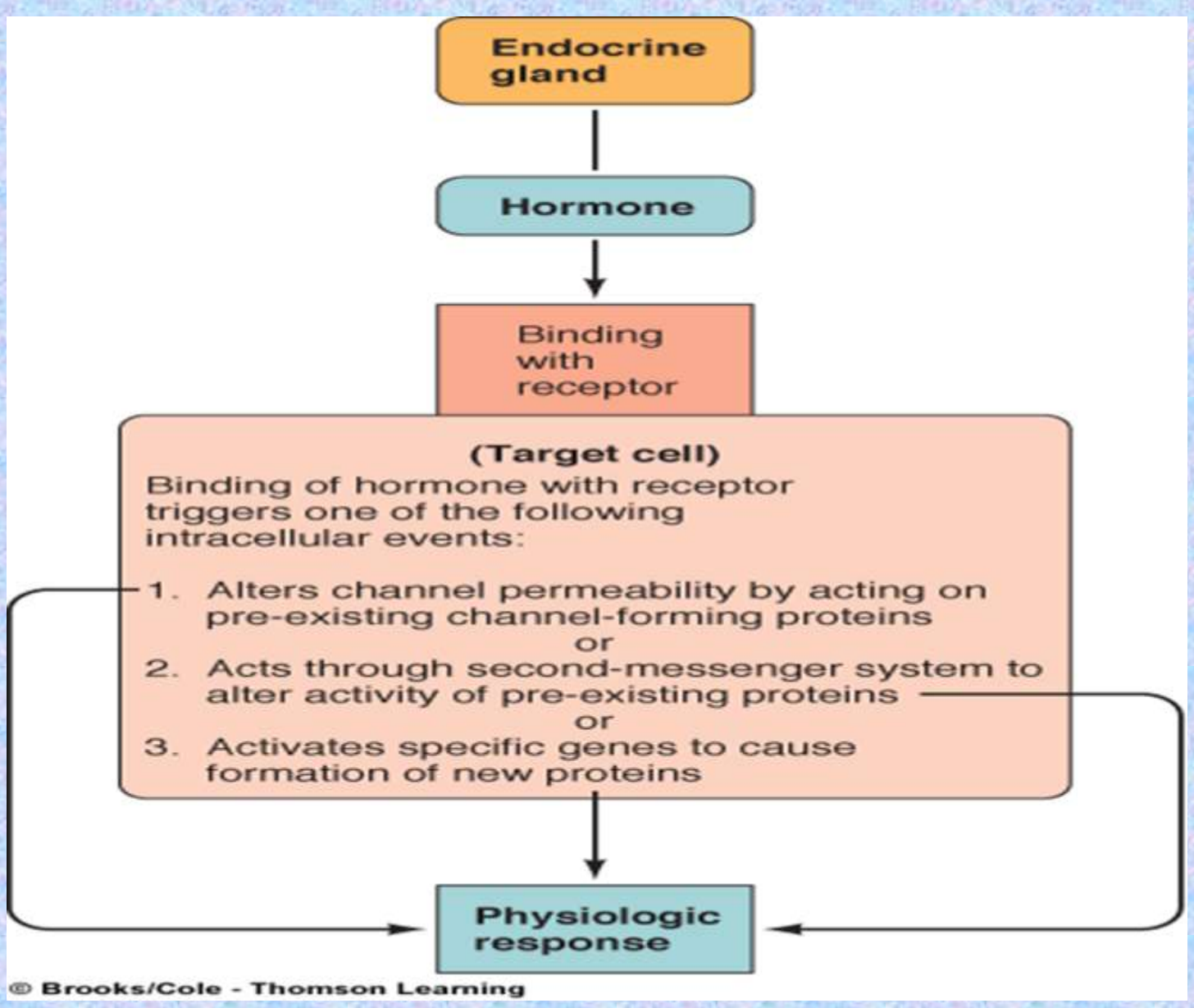
CYTOPLASMIC RECEPTOR

- **Receptors present in cell cytoplasm**
- E.g., Steroid hormones.

NUCLEAR RECEPTOR

- **Receptors present in nucleus & there is direct association with one or more chromosomes.**

- E.g., Thyroid hormones, Retinoid hormones, Vitamin-D.


Endocrine gland
Hormone
Binding with receptor
(Target cell)
Binding of hormone with receptor triggers one of the following intracellular events:
1. Alters channel permeability by acting on pre-existing channel-forming proteins
or
2. Acts through second-messenger system to alter activity of pre-existing proteins
or
3. Activates specific genes to cause formation of new proteins
Physiologic response
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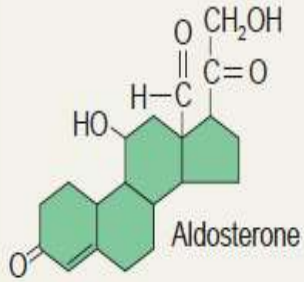
LIPID-SOLUBLE HORMONES

TABLE 18.2

Summary of Hormones by Chemical Class

CHEMICAL CLASS	HORMONES	SITE OF SECRETION
LIPID-SOLUBLE		
Steroid hormones	Aldosterone, cortisol, and androgens.	Adrenal cortex.
 Aldosterone	Calcitriol.	Kidneys.
	Testosterone.	Testes.
	Estrogens and progesterone.	Ovaries.
Thyroid hormones	T_3 (triiodothyronine) and T_4 (thyroxine).	Thyroid gland (follicular cells).
 Triiodothyronine (T_3)		
Gas	Nitric oxide (NO).	Endothelial cells lining blood vessels.

HOW LIPID-SOLUBLE HORMONES WORK?

- **Binding to specific cell receptor in the cell membrane and form hormone-cell receptor complex, which diffuses to nucleus**
- **The receptor is eventually released for re-use**
- **Steroid activates a specific gene to produce mRNA**
- **mRNA pass out into the cytoplasm and initiates protein [enzyme] synthesis**

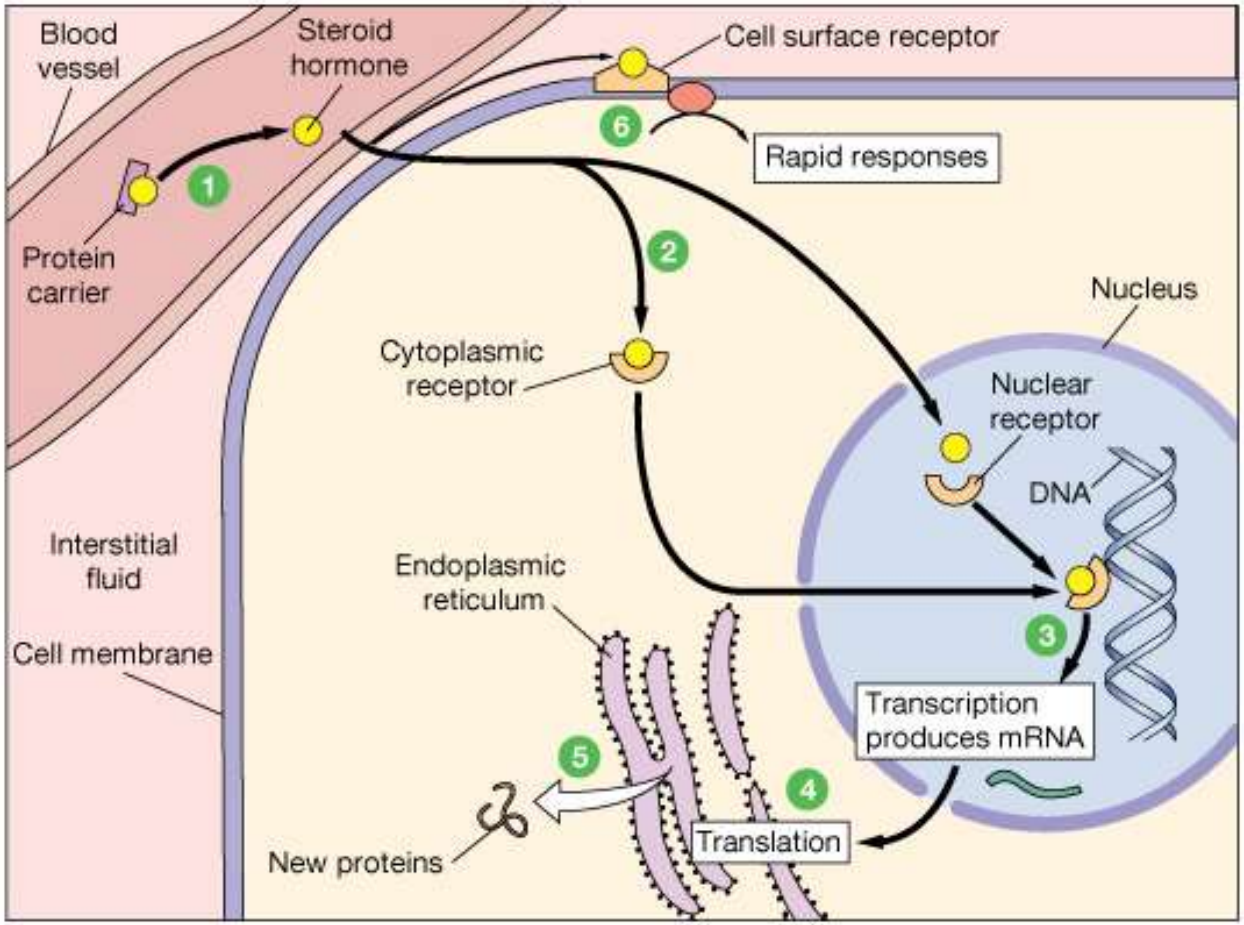
❖ **why do they penetrate the cell?**

✓ **the whole process is called mobile-receptor hypothesis** in which a steroid hormone is not attached to the plasma membrane, but seem to move freely in the nucleoplasm

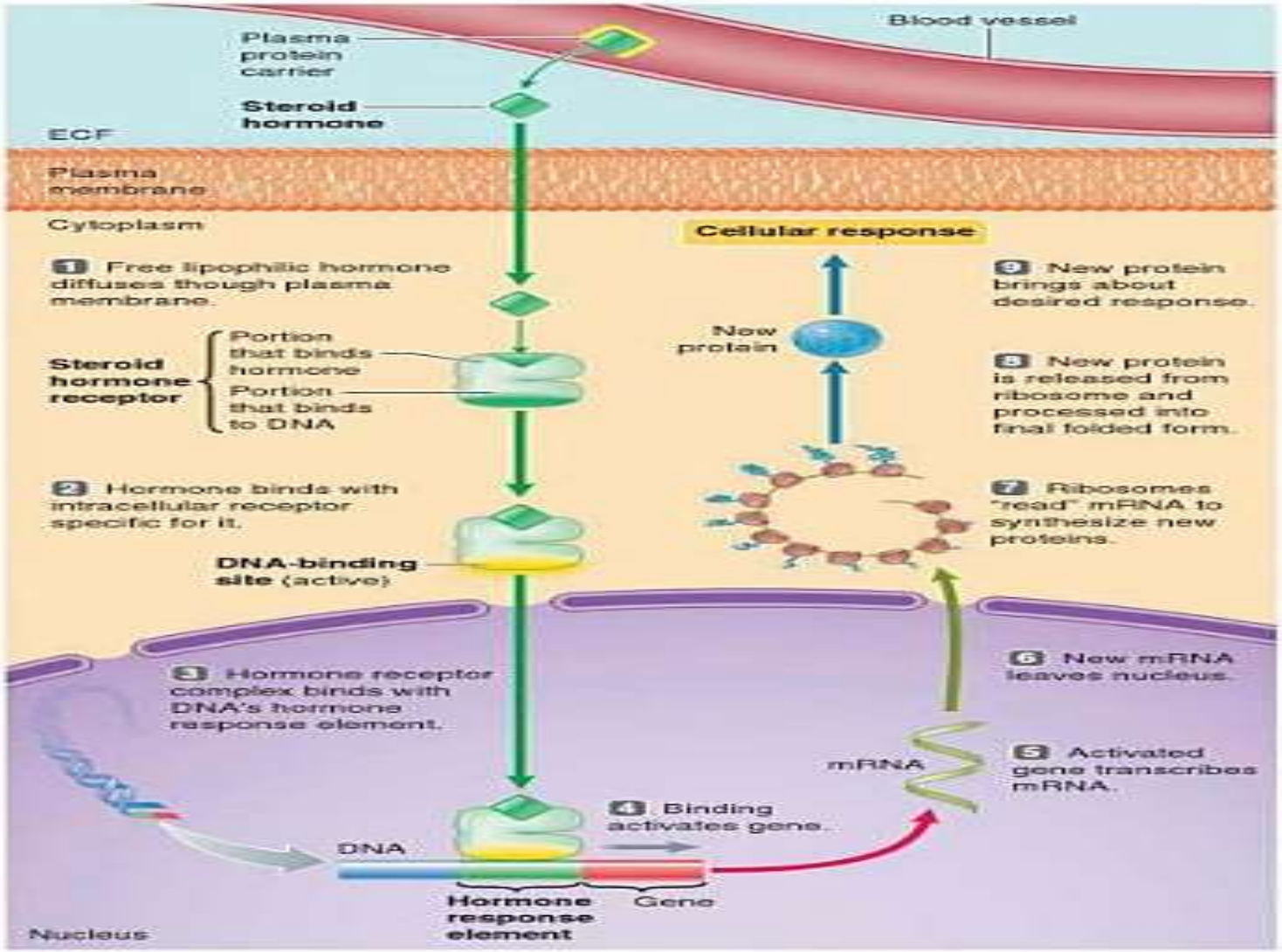
HOW LIPID-SOLUBLE HORMONES WORK?

- **Step1:** Free lipophilic hormone (hormone not bound with its plasma protein carrier) diffuses through the plasma membrane of the target cell and binds with the receptor which is intracellularly located inside the cytosol/or in the nucleus.
- **Step2.** Each receptor has specific binding region with hormone and another region with binding with DNA. Receptor alone cannot bind to DNA unless it binds to hormone. Once the hormone is bound to receptor, the hormone receptor complex binds to specific region of DNA known as **Hormone response element(HRE**).
- **Step3:** Transcription of gene
- **Step4:** m RNA transported out of nucleus into the cytoplasm
- **Step5:** Translation at Ribosome
- **Step6:** Protein/enzyme released from ribosome
- **Step7:** protein/enzyme mediate ultimate response

STEROID HORMONES: MOLECULAR ACTION

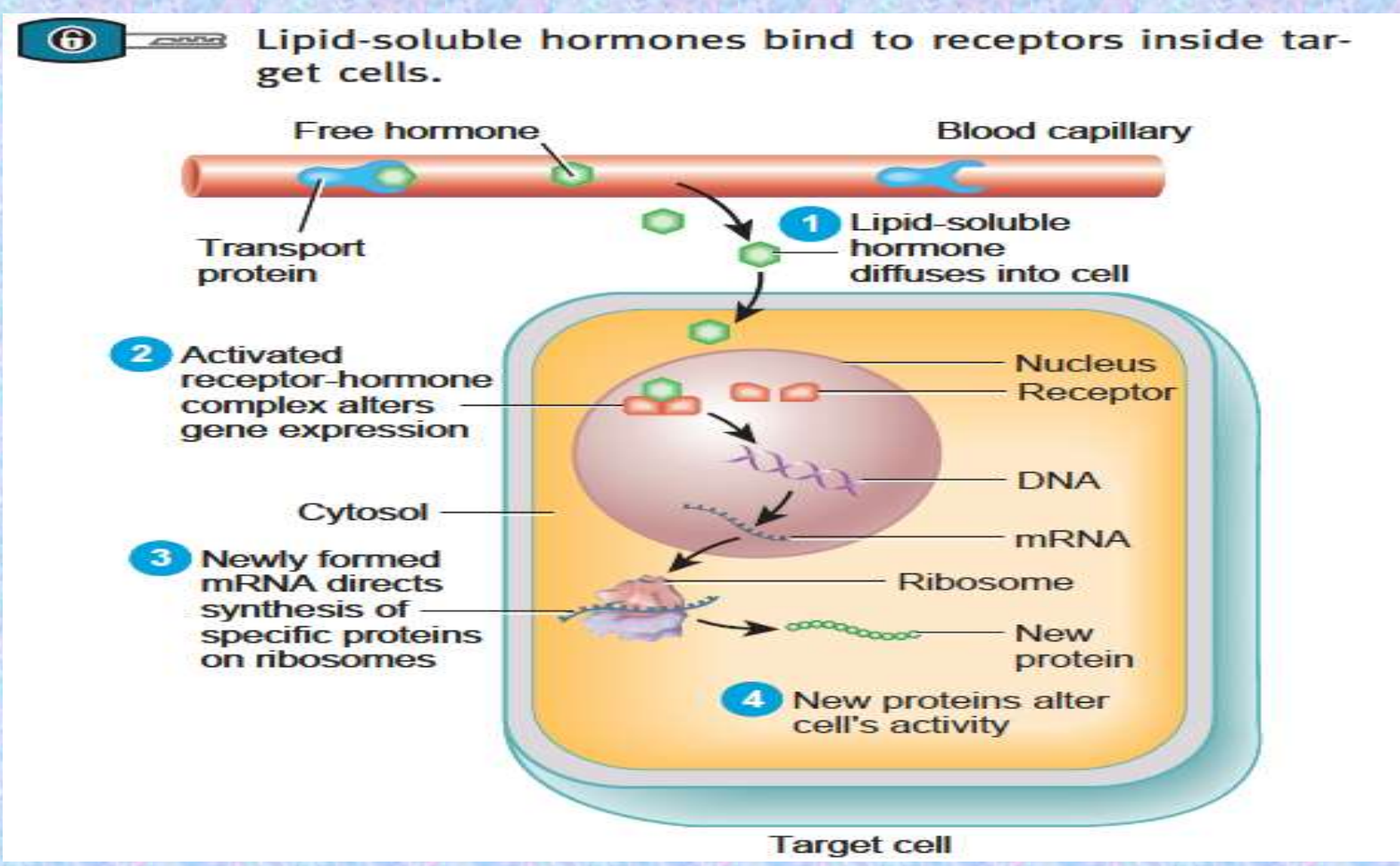


1. Most hydrophobic steroids are bound to plasma protein carriers. Only unbound hormones can diffuse into the target cell.
2. Steroid hormone receptors are in the cytoplasm or nucleus.
3. The receptor-hormone complex binds to DNA and activates or represses one or more genes.
4. Activated genes create new mRNA that moves back to the cytoplasm.
5. Translation produces new proteins for cell processes.
6. Some steroid hormones also bind to membrane receptors that use second messenger systems to create rapid cellular responses.

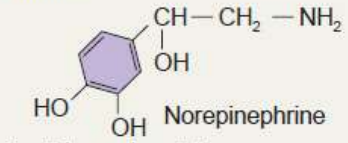
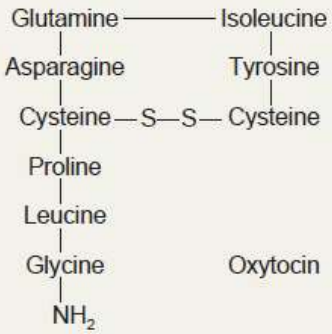
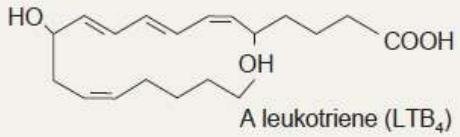


Lipophilic hormone response mediated through Cytosolic receptor/nuclear receptor

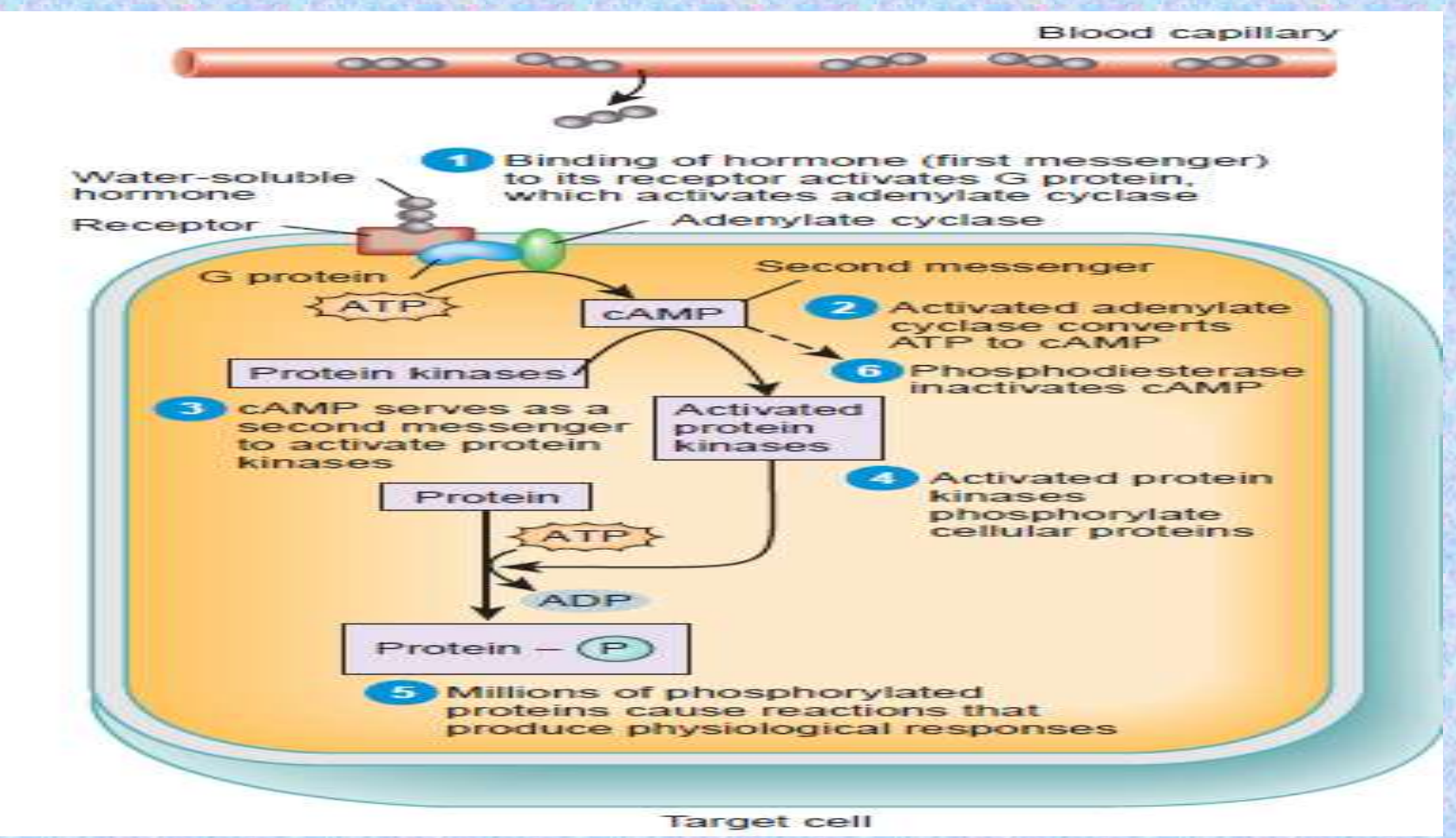
HOW LIPID-SOLUBLE HORMONES WORK?



WATER-SOLUBLE HORMONES

WATER-SOLUBLE		
Amines  Norepinephrine	Epinephrine and norepinephrine (catecholamines).	Adrenal medulla.
	Melatonin.	Pineal gland.
	Histamine.	Mast cells in connective tissues.
	Serotonin.	Platelets in blood.
Peptides and proteins  Oxytocin	All hypothalamic releasing and inhibiting hormones.	Hypothalamus.
	Oxytocin, antidiuretic hormone.	Posterior pituitary.
	Human growth hormone, thyroid-stimulating hormone, adrenocorticotropic hormone, follicle-stimulating hormone, luteinizing hormone, prolactin, melanocyte-stimulating hormone.	Anterior pituitary.
	Insulin, glucagon, somatostatin, pancreatic polypeptide.	Pancreas.
	Parathyroid hormone.	Parathyroid glands.
	Calcitonin.	Thyroid gland (parafollicular cells).
	Gastrin, secretin, cholecystokinin, GIP (glucose-dependent insulinotropic peptide).	Stomach and small intestine (enteroendocrine cells).
	Erythropoietin.	Kidneys.
	Leptin.	Adipose tissue.
Eicosanoids  A leukotriene (LTB_4)	Prostaglandins, leukotrienes.	All cells except red blood cells.

HOW WATER-SOLUBLE HORMONES WORK?



HOW WATER-SOLUBLE HORMONES WORK?

- ●**1 A water-soluble hormone (the first messenger) diffuses from** the blood through interstitial fluid and then binds to its receptor at the exterior surface of a target cell's plasma membrane. The hormone–receptor complex activates a membrane protein called a **G protein. The activated G protein** in turn activates **adenylate cyclase.**

- ●**2 Adenylate cyclase converts ATP into cyclic AMP (cAMP).** Because the enzyme's active site is on the inner surface of the plasma membrane, this reaction occurs in the cytosol of the cell.

- ●**3 Cyclic AMP (the second messenger) activates one or more** protein kinases, which may be free in the cytosol or bound to the plasma membrane. A **protein kinase is an enzyme** that phosphorylates (adds a phosphate group to) other cellular proteins (such as enzymes). The donor of the phosphate group is ATP, which is converted to ADP.

HOW WATER-SOLUBLE HORMONES WORK?

- ●4 Activated protein kinases phosphorylate one or more cellular proteins. Phosphorylation activates some of these proteins and inactivates others, rather like turning a switch on or off.
- ●5 Phosphorylated proteins in turn cause reactions that produce physiological responses. Different protein kinases exist within different target cells and within different organelles of the same target cell. Thus, one protein kinase might trigger glycogen synthesis, a second might cause the breakdown of triglyceride, a third may promote protein synthesis, and so forth. As noted in step ●4 phosphorylation by a protein kinase can also inhibit certain proteins. For example, some of the kinases unleashed when epinephrine binds to liver cells inactivate an enzyme needed for glycogen synthesis

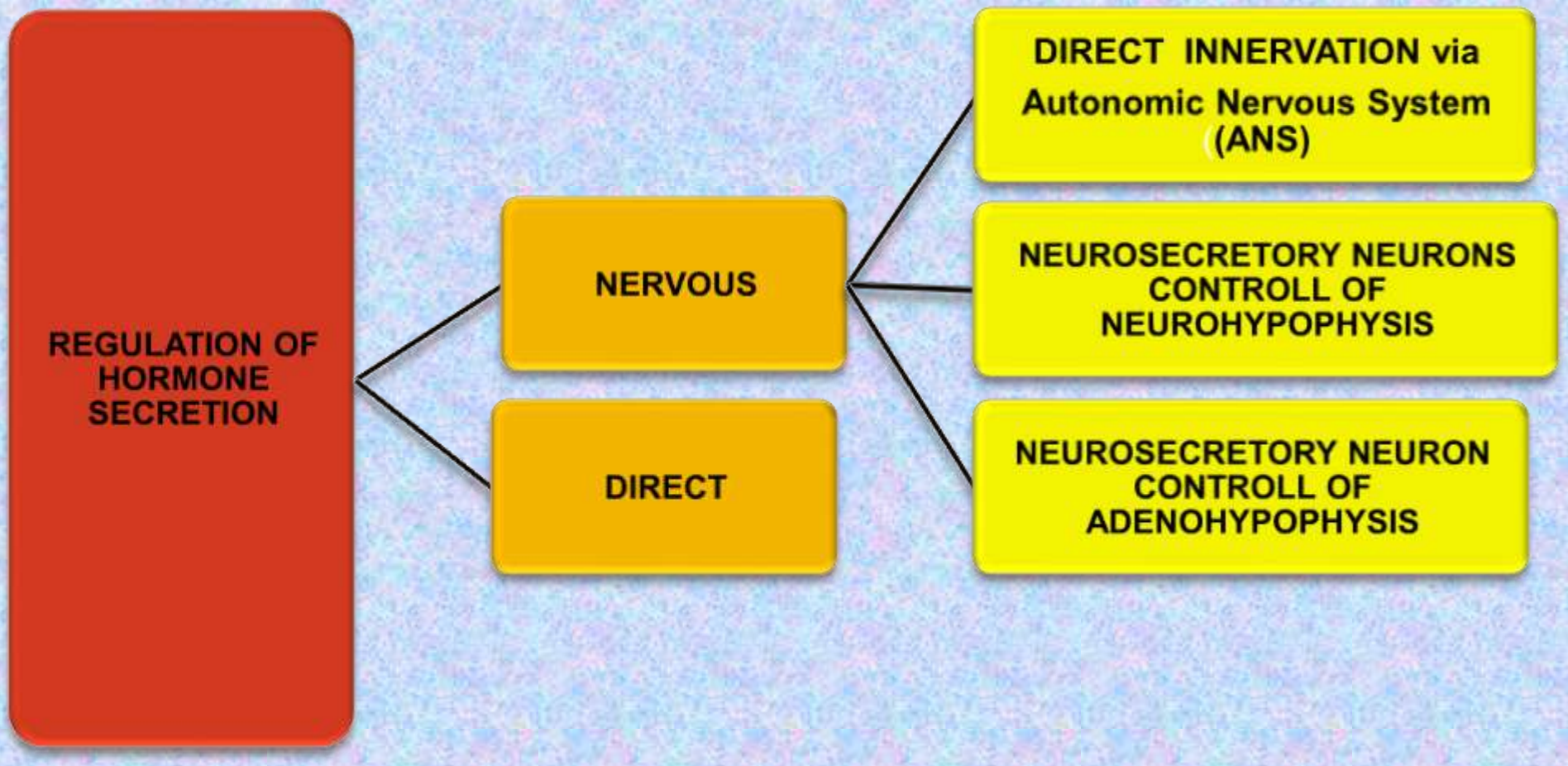
.

- ●6 After a brief period, an enzyme called phosphodiesterase inactivates cAMP. Thus, the cell's response is turned off unless new hormone molecules continue to bind to their receptors in the plasma membrane

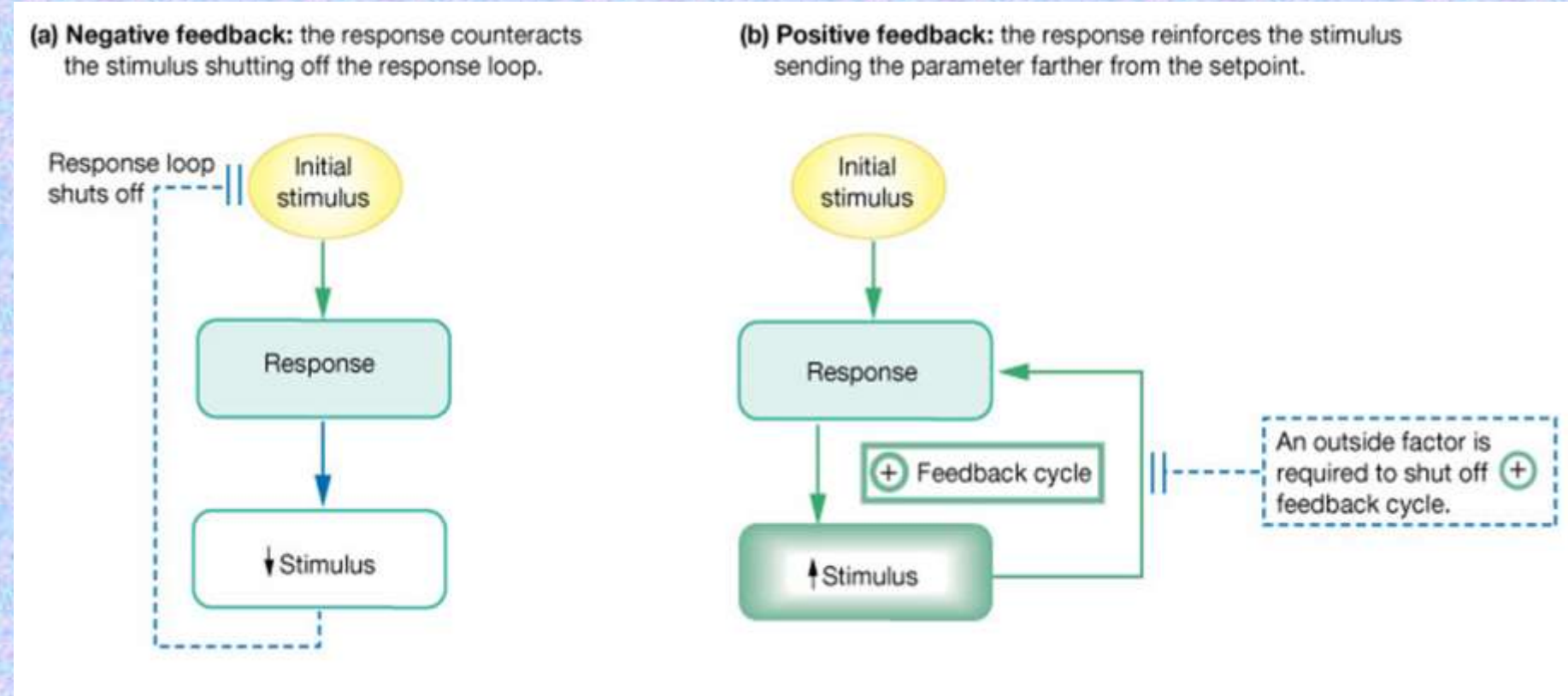
HOW WATER-SOLUBLE HORMONES WORK?

- **The whole process above is called SECOND MESSENGER MECHANISM also called FIXED-MEMBRANE-RECEPTOR HYPOTHESIS. In this instance, the first messenger delivers message to fixed receptors in the target cell's plasma membrane. The message then is passed to the cell where second messenger triggers appropriate cellular changes**

REGULATION OF HORMONE SECRETION



FEEDBACK CONTROL



FEEDBACK CONTROL

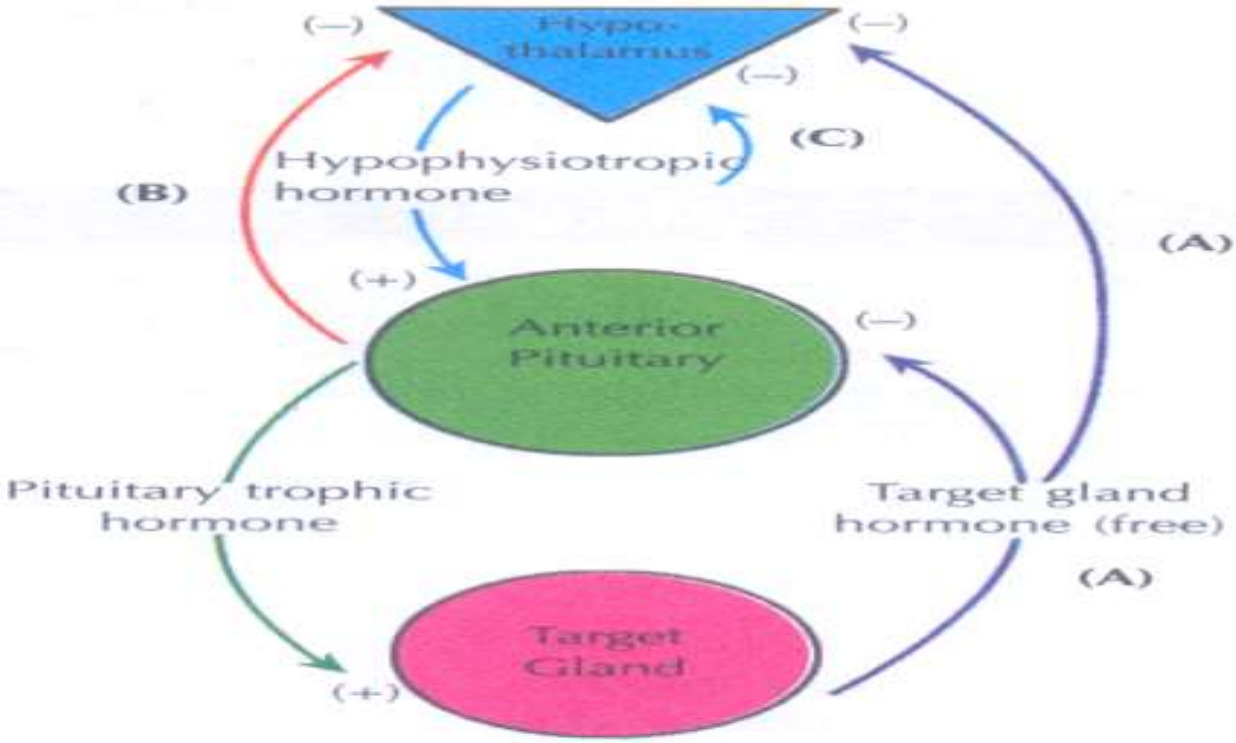


Fig. 9.1.6 Negative 'feedback control' of hormone secretion. long loop (A); short loop (B) and ultra-short loop (C) feedback mechanisms. {(+): stimulation; (–): negative feedback control mechanism}

- ve feedback control

+ ve feedback

Thank you