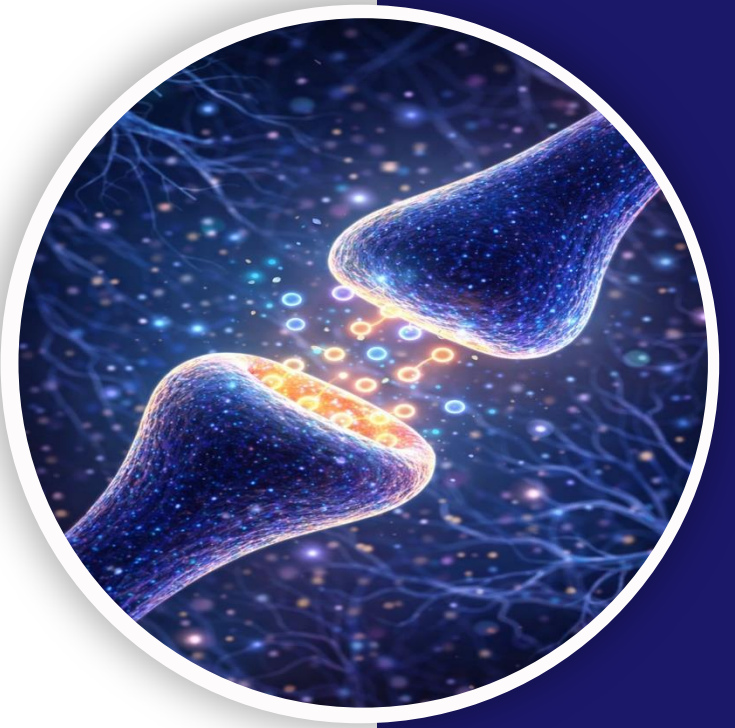
بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Physiology | MID L1+2

Introduction to Endocrinology



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Objectives

- Differentiate endocrine system and nervous system
- Define hormone
- List the types of hormones
- Follow up the mechanism of action of hormones
- Explain hormone regulation mechanism

Comparison between Nervous and Endocrine Control System

- Nervous system is **fast** compared to endocrine, it is obvious that **direct effectivity of neurons** is **faster** than the endocrine system, as hormones **spend more time traveling in the blood** until reaching the targeted cells, and acting on receptors, along with the production of 2nd messenger, and the pathway that ends in the production of the last effect.
- **Nervous system** uses **Action Potentials** compared to chemicals (Hormones) the **endocrine system uses**.
- Nervous system has **lower gain compared to very high gain for the Endocrine system.** **Gain** tells you **how good a control system is at correcting an error**, it measures how strongly the system brings a variable back to normal after a disturbance. Higher gain means more complete correction, meaning that although **endocrine system takes more time to exert its effect, it usually results in a much better correction when compared to the nervous system (a correction that is closer to the normal value).**

$$Gain = \frac{Correction}{Error}$$

- **Nervous system affects skeletal muscle and glands secretion**, but the **endocrine affects growth, metabolism and reproduction.**

Further explanation of Gain

$$Gain = \frac{Correction}{Error}$$

- Let's have an example using the formula above, if the normal blood pressure (MAP) is 100 mmHg and a disturbance increases it to 120 mmHg, the nervous system might correct it to 105 mmHg, this means that the correction is 15 mmHg and the error is 5 mmHg, so the gain is 15 ÷ 5 = 3, on the other hand, the endocrine system might correct it to 100.001 mmHg, this is a correction of approximately 20 mmHg and an error of approximately 0 mmHg, giving a very high gain that approaches infinity.
- **This shows that the nervous system is faster but less accurate (low gain), while the endocrine system is slower but much more precise (high gain).**

Example:

- Normal MAP = **100 mmHg**
- Disturbance raises MAP to **120 mmHg**

Nervous system:

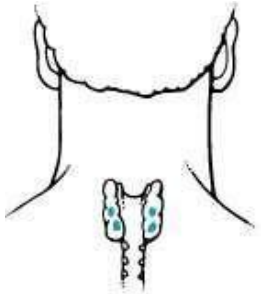
- Corrects to **105 mmHg**
  - Correction = 15
  - Error = 5
  - **Gain = 15 ÷ 5 = 3**

Endocrine system:

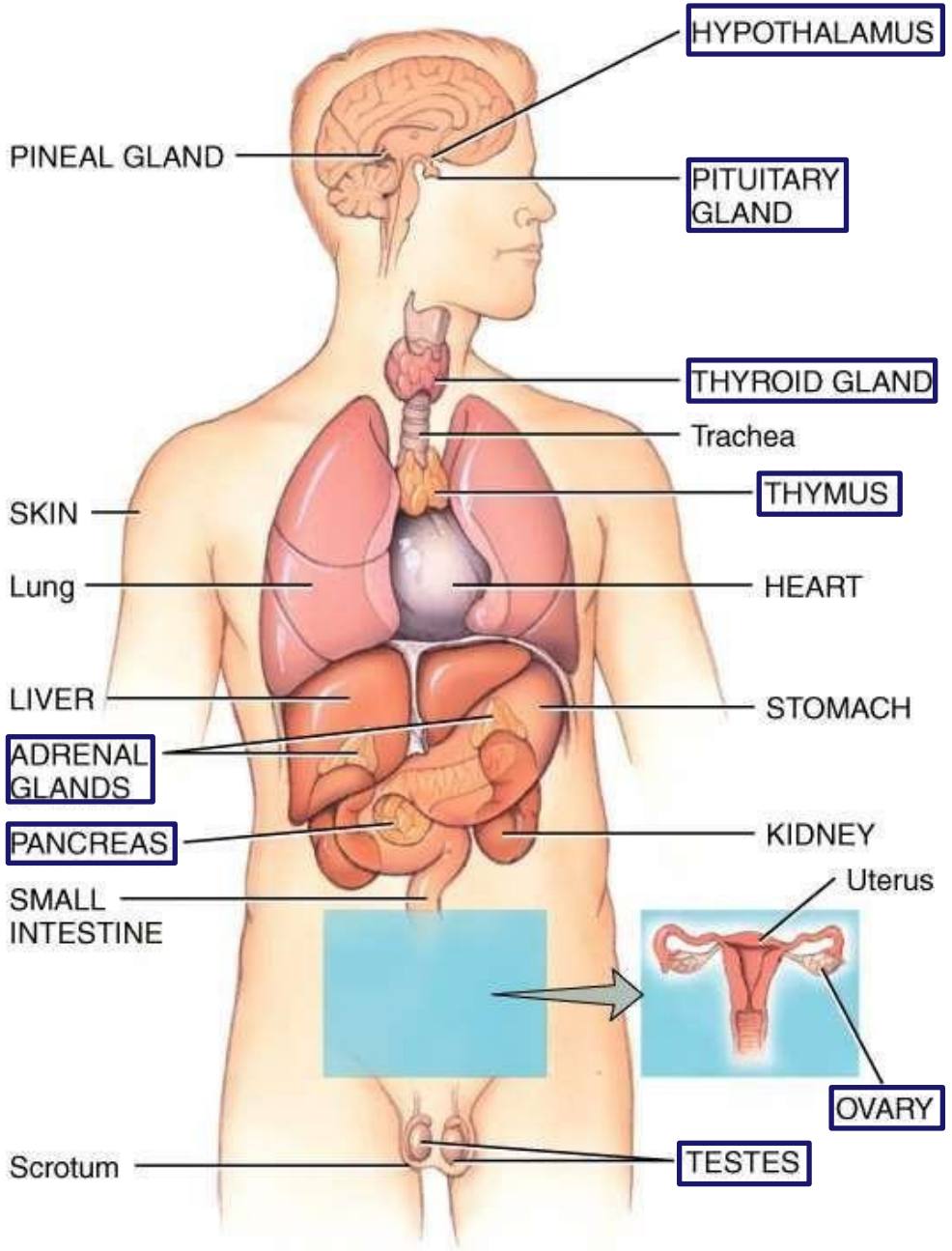
- Corrects to **100.001 mmHg**
  - Correction ≈ 20
  - Error ≈ 0
  - **Gain = 20 ÷ ~0 = ∞ (very high gain)**

✅ **Interpretation:**

- **Nervous system** = **low gain** (quick, less accurate correction)
- **Endocrine system** = **very high gain** (slower, but almost perfect correction)



PARATHYROID GLANDS (behind thyroid glands)



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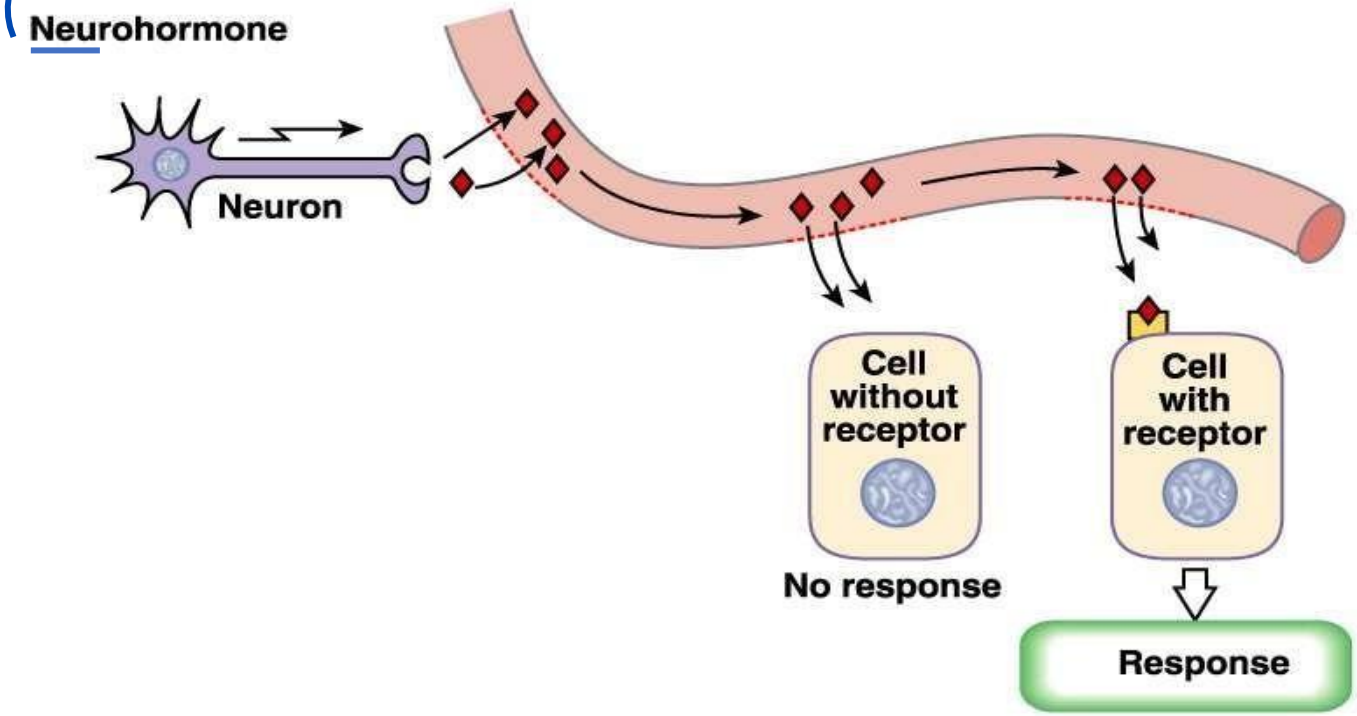
Endocrine Glands and Hormones

- Hormones are molecules that have an effect on specific organs.
- Neurohormones: are hormones that are secreted from neurons, If they are released into the synaptic cleft, they can also be referred to as neurotransmitters.
- Specialized neurons that secrete chemicals into the blood rather than synaptic cleft.
  - Chemical secreted is called neurohormone e.g. ADH and oxytocin that are secreted from the posterior pituitary gland.
- Hormones:
  - **Affect metabolism** of target organs.
    - Help regulate total body metabolism, growth, and reproduction.

As it is secreted from a neuron.

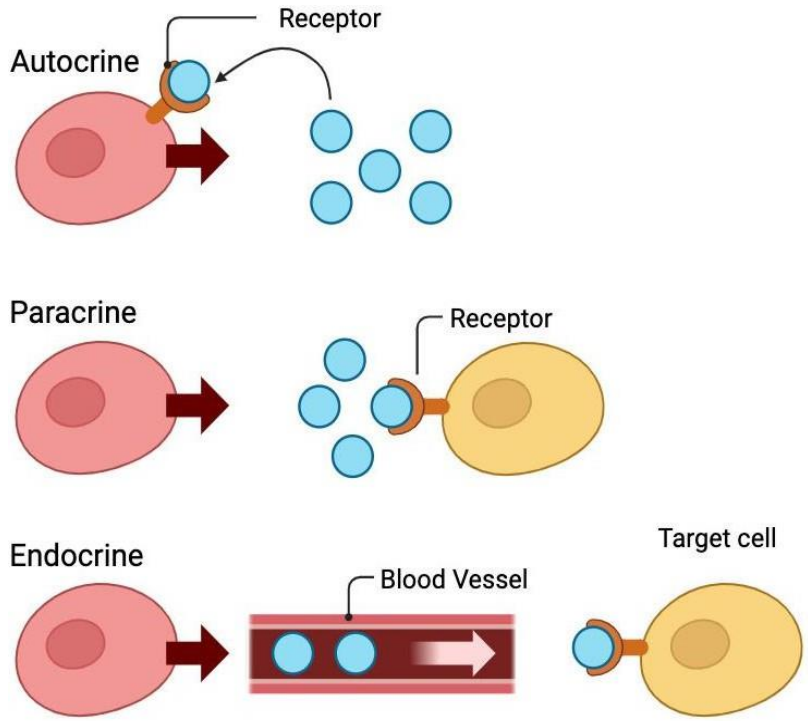


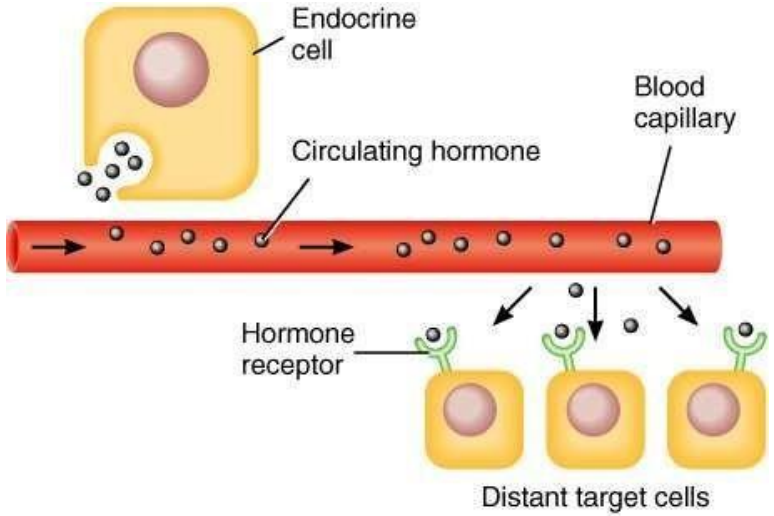
→ The effect of hormones is tied to the presence of specific receptors for the hormone; ***without the presence of these receptors the hormones won't be able to exert their effect.***

Hormone types:

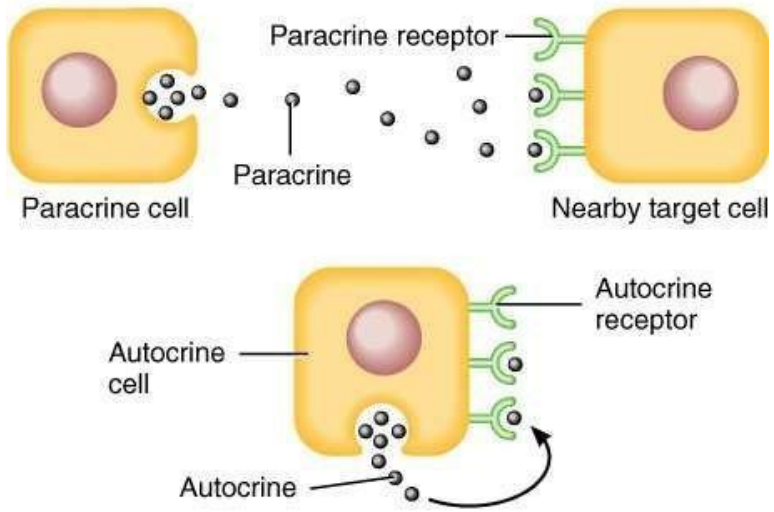
- Circulating hormones (**endocrine** hormones): circulate in the blood throughout body, glands that have secreted these hormones are far away from the targeted cells.
- Local hormones (**paracrine** and **autocrine** hormones) - act locally
  - Paracrine – act on neighboring cells
  - Autocrine – act on the same cell that secreted them

The next 4 slides have figures that help clarify each type, make sure to have a look on them.





(a) Circulating hormones



(b) Local hormones (paracrines and autocrines)

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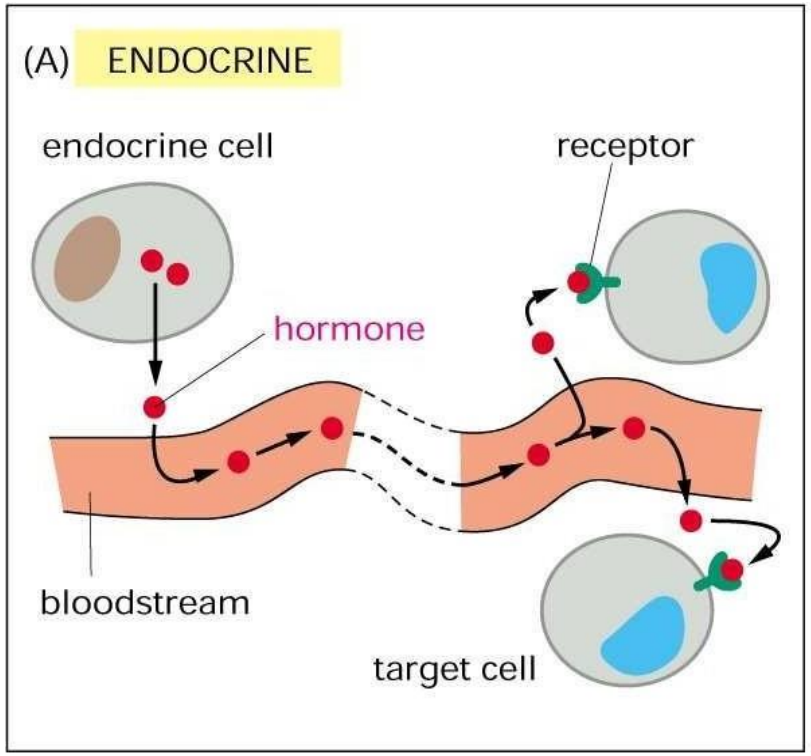
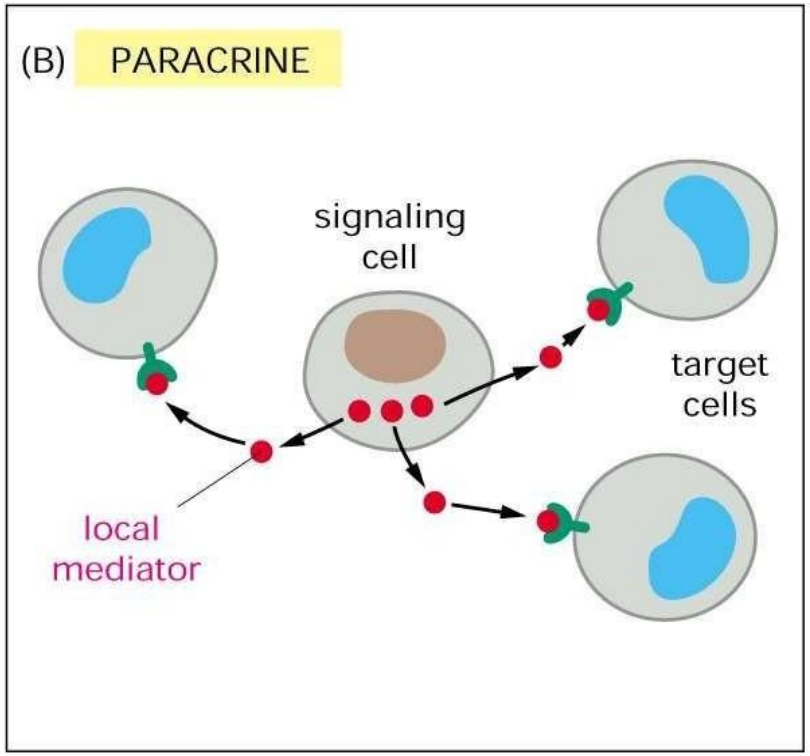
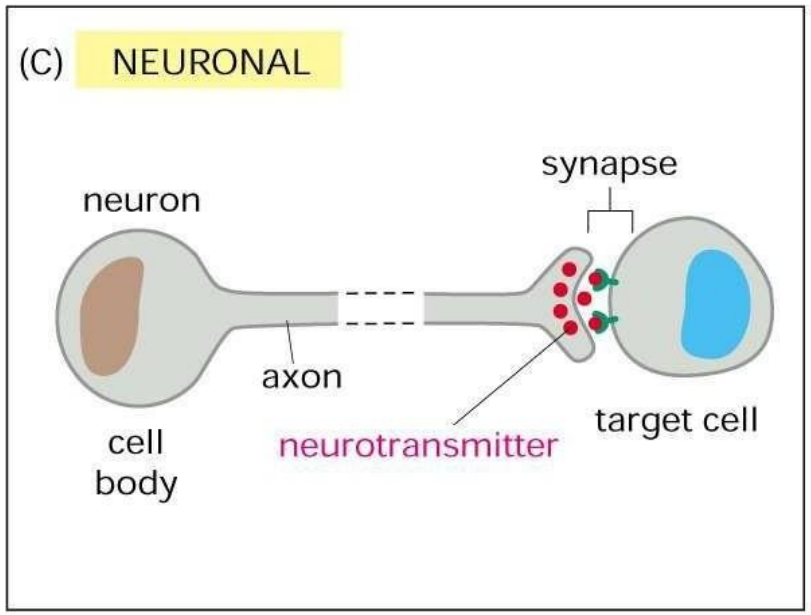
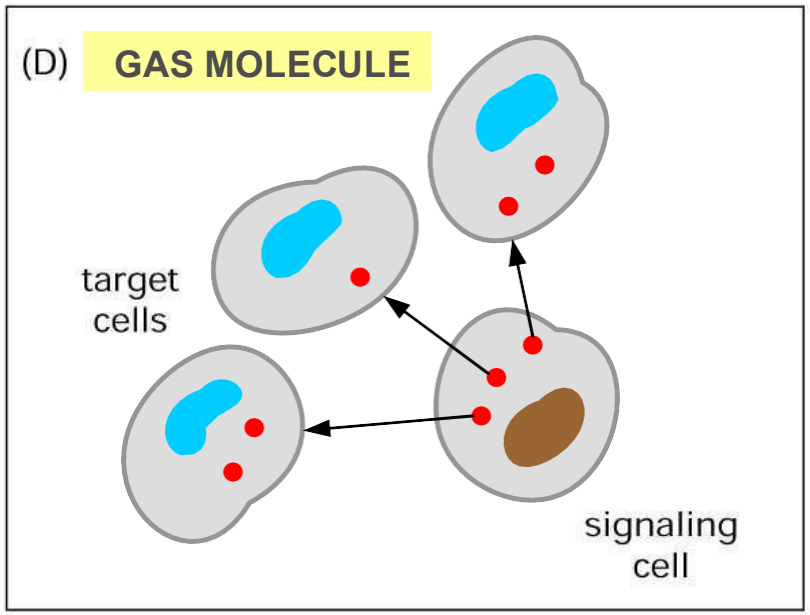
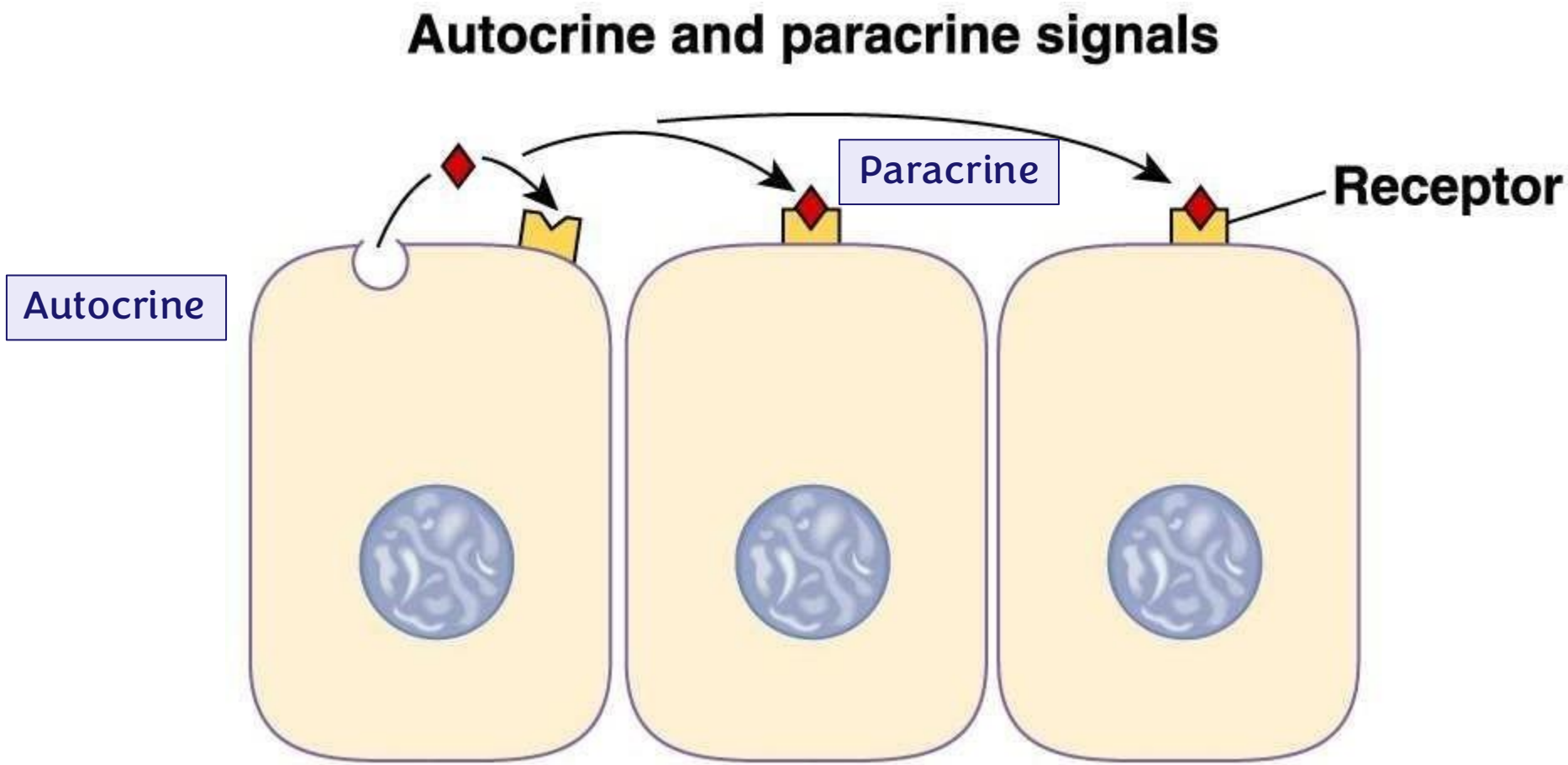




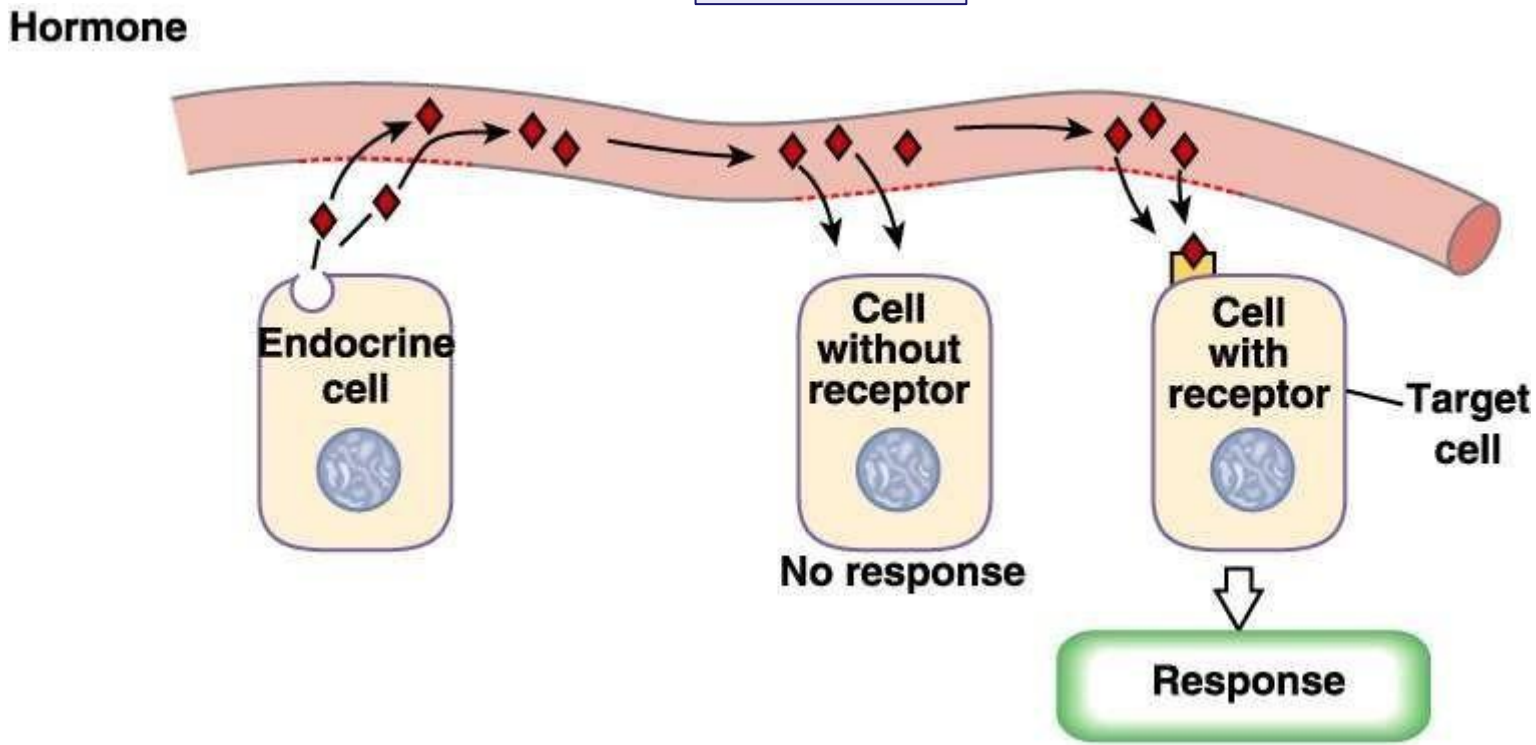




Gas molecules may also act on distant cells, but usually they act on the nearby cells.


Autocrine and paracrine signals
Paracrine
Receptor
Autocrine

Endocrine


Hormone
Endocrine cell
Cell without receptor
No response
Cell with receptor
Target cell
Response

Chemical classes of hormones

- **Lipid-soluble hormones:** need transport proteins to be able to get transported through the blood, these transport proteins **could be non-specific** such as albumin **or specific** such as globulins.

Lipid soluble hormones include:

- Steroid Hormones (steroids): Lipids derived from cholesterol and are lipophilic hormones, they are mainly excreted from the gonads and the adrenal cortex, they include:
  - Testosterone.
  - Estradiol.
  - Cortisol. (Corticosteroids in general)
  - Progesterone.

- Thyroid, secreted from the thyroid gland.
- Nitric oxide (NO), it is a gas hormone, so it is lipophilic and doesn't need transport proteins.

Chemical classes of hormones

- Water-soluble – circulate in "free" form in the plasma, examples include:
  - **Amines**:
    - Hormones derived from tyrosine and tryptophan.
    - Norepinephrine, Epinephrine, T_4 –tetraiodothyronine (T_4, also known as thyroxine **is lipid soluble even though it is derived from tyrosine**)
  - **Polypeptides and proteins:**
    - **Polypeptides**:
      - Chains of **< 100** amino acids in length.
        - **ADH**. (**A**nti**d**iuretic **h**ormone, also called vasopressin)
      - **Protein hormones:**
      - Polypeptide chains with **> 100** amino acids.
      - Growth hormones that are secreted from the anterior pituitary and prolactin that is essential for lactation.
  - Eicosanoid (prostaglandins, arachidonic acid-derived hormones)

Chemical Classes of Hormones

- Glycoproteins:
  - Long polypeptides (>100) bound to 1 or more carbohydrate (CHO) groups, Ex:
    - FSH (follicular stimulating hormone) and LH (luteinizing hormone), both are secreted from the anterior pituitary, **they exert their effect on the gonads**, they are also called **gonadotropins**, TSH (Thyroid stimulating hormone) and hCG (human Chorionic Gonadotropin) that is secreted by the placenta during pregnancy.

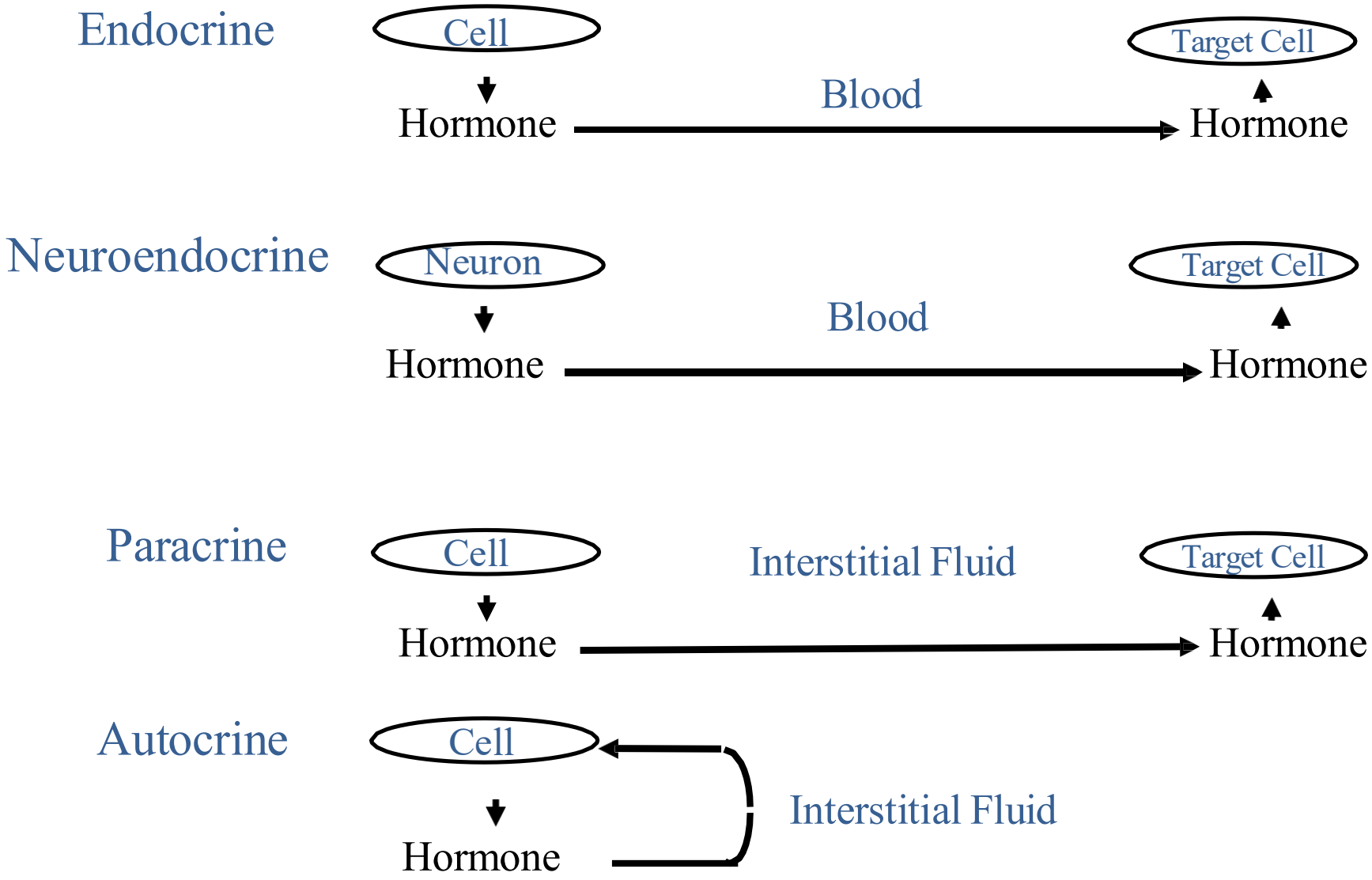
      They are made of: **α subunit** that is shared by all glycoproteins and **β subunit** which is hormone-Specific and differs according to the type of hormone, **pregnancy tests detects β subunit of hCG in urine or blood.**
- Hormones can also be divided into:
  - Polar:
    - H_20 soluble.
  - Nonpolar (lipophilic):
    - H_20 insoluble.
      - Can gain entry into target cells.
      - Steroid hormones and T_4.

Prohormones and Prehormones

- Prohormones: (hormone precursors, converted into hormones by post-translational modification)
  - Precursor is a longer chained polypeptide that is cut and spliced together to make the hormone, examples include:
    - Proinsulin and Prothyroxine
- Preprohormones: (prohormone precursors, cut and spliced in the endoplasmic reticulum to be converted into prohormones, prohormones then get converted into hormones by post-translational modification that takes place in the Golgi-apparatus)
  - Prohormone derived from larger precursor molecule.
    - Preproinsulin → Proinsulin → Insulin
- Prehormones:
  - Molecules secreted by endocrine glands that are inactive until changed into hormones by the target cells.
    - T_4 converted to T_3 by the enzyme deiodase, T_3 is 4-5 times more active than T_4.

- Pre-hormones are hormones that are secreted by glands in an **inactive or less active form**. They circulate in the blood and only become **fully active after they are converted by enzymes in target tissues**. This extra step allows the body to fine-tune when and where the hormone takes effect, adding **an extra layer of regulation**.

Intercellular Communication



Classes of Hormones

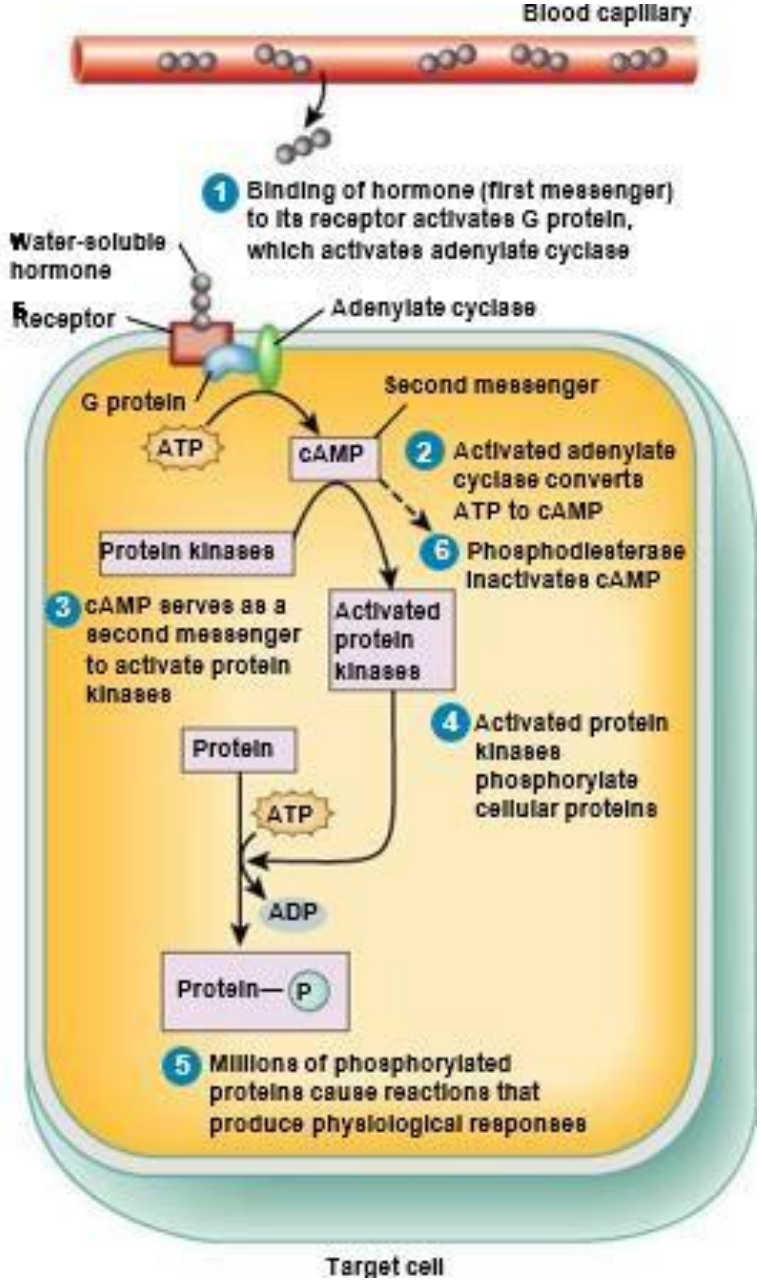
- Peptide & Protein Hormones
- Steroid Hormones
- Amine Hormones
- Gas : Nitric Oxide (NO) and CO

Water-soluble Hormones

- **Water-soluble hormone** (the first messenger) binds to its specific **membrane receptor** on the target cell, if this receptor is a G-protein coupled receptor, binding of the hormone will induce a conformational change in the receptor that activates a nearby **G protein which** is a heterotrimer composed of **α (alpha), β (beta), and γ (gamma) subunits**. Upon activation, **GDP is replaced with GTP** on the α subunit, causing the **α subunit to dissociate** from the βγ complex. The **GTP-bound α subunit** then activates the enzyme **adenylate cyclase**, which catalyzes the conversion of **ATP to cyclic AMP (cAMP)** – the second messenger.

- cAMP then activates **protein kinase A (PKA),** these active kinase units **phosphorylate specific cellular proteins**, using ATP to transfer phosphate groups. This phosphorylation could activate or inhibit other proteins or enzymes; phosphorylation cascade **amplifies** the signal; one hormone receptor interaction can lead to the activation of thousands of proteins through sequential kinase activation.

- Eventually, the signal is **terminated** by two main mechanisms:
  1. **Phosphodiesterase (PDE)** breaks down cAMP into AMP, stopping PKA activation.
  2. The **GTP on the α subunit is hydrolyzed to GDP**, which inactivates the G protein and causes re-association with the βγ subunits, stopping further stimulation of adenylate cyclase.



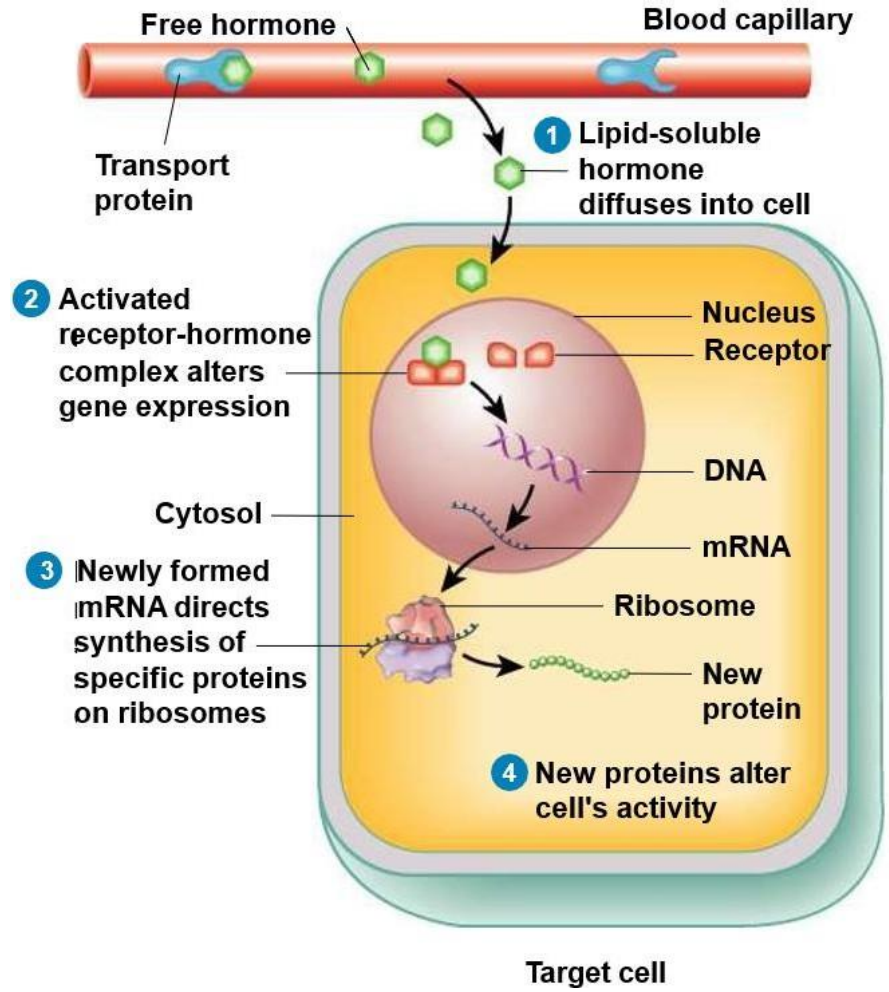
Lipid-soluble Hormones

- **Lipid-soluble hormones**, such as **steroid** hormones and **thyroid** hormones, circulate in the blood bound to **transport proteins**. Once they dissociate from their carrier and become **free hormones, they** can diffuse through the **phospholipid bilayer** of the target cell's membrane (since they are lipid soluble).

- Once inside the cell, the hormone binds to **intracellular receptors** located either in the **cytosol or nucleus**. This binding forms a **receptor-hormone complex**, which then interacts directly with specific DNA sequences in the nucleus, **modifying gene expression** by acting as a transcription factor.

- The activated DNA is transcribed into **messenger RNA (mRNA)**, which exits the nucleus and binds to **ribosomes** in the cytoplasm. These ribosomes use the mRNA template to **synthesize new proteins**, which are usually enzymes or structural proteins. These newly formed proteins then **alter the cell's physiological activity**, leading to the hormone's specific effect.

- This mechanism is **slower** than that of water-soluble hormones but results in **longer-lasting changes**, as it directly affects gene transcription and protein synthesis.



Activating already made enzymes would always be faster than synthesizing the proteins from scratch

Peptide & Protein Hormones

Gland/Tissue	Hormones	Gland/Tissue	Hormones
Hypothalamus	• TRH, GnRH, CRH GHRH, Somatostatin(GHIH)	Placenta	• HCG, HCS or HPL
Anterior pituitary	• ACTH, TSH, FSH, LH, PRL, GH	Kidney	• Renin
Posterior pituitary	• Oxytocin, ADH	Heart	• ANP
Thyroid	• Calcitonin	G.I. tract	• Gastrin, CCK, Secretin, GIP, Somatostatin, GLP-1
Pancreas	• Insulin,Glucagon, Somatostatin		
Liver (under the effect of GH)	• Somatomedin C (IGF-1)	Adipocyte	• Leptin
Parathyroid	• PTH		

Peptide & Protein Hormones

- Hypothalamus, *secretes either stimulating or inhibiting hormones*
  - **TRH** - Thyrotropin-releasing hormone, the smallest peptide composed of 3 amino acids.
  - **GnRH** - Gonadotropin-releasing hormone
  - **CRH** - Corticotropin-releasing hormone
  - **GHRH** - Growth hormone-releasing hormone
  - **Somatostatin (GHIH)** - Growth hormone-inhibiting hormone
- Anterior pituitary
  - **ACTH** - Adrenocorticotropic hormone, acts on the adrenal cortex
  - **TSH** - Thyroid-stimulating hormone, acts on the thyroid gland
  - **FSH** - Follicle-stimulating hormone (works on gonads for female and male)
  - **LH** - Luteinizing hormone (work on gonads for female and male
  - **PRL** - Prolactin, a protein
  - **GH** - Growth hormone
- Posterior pituitary
  - **Oxytocin**(8 amino acid peptide)
  - **ADH** - Antidiuretic hormone (also called vasopressin) (8 amino acid peptide)

Peptide & Protein Hormones

- Thyroid gland
  - Calcitonin, secreted from parafollicular cells of the thyroid gland, it has a role in calcium homeostasis, but its not secreted from same area where T3 and T4 are secreted).
- Parathyroid gland
  - **PTH** - Parathyroid hormone.
- Pancreas (islets of Langerhans)
  - **Insulin**
  - **Glucagon**
  - **Somatostatin**

  → Responsible of glucose homeostasis.
- Liver
  - **Somatomedin C (IGF-1)** - Insulin-like growth factor 1, secreted from the liver after it is stimulated with growth hormones.
- Placenta
  - **hCG** - Human chorionic gonadotropin.
  - **hCS / hPL** - Human chorionic somatomammotropin / Human placental lactogen.

Peptide & Protein Hormones

- Kidney
  - Renin, an enzyme that converts angiotensinogen into angiotensin 1.
- Heart
  - ANP, Atrial Natriuretic Peptide, secreted from the atria of the heart (28 amino acid peptide)
- GI tract (all are peptides)
  - Gastrin
  - CCK, cholecystokinin
  - Secretin
  - GIP, Gastric Inhibitory Peptide
  - GLP-1, Glucagon-Like Peptide 1
- Adipocytes
  - Leptin

POMC is a very large hormone, formed in ER and sent to Golgi to slice it and to do post translational modification to produce 3 hormones:
1) ACTH 2) MSH 3) beta endorphins

Examples of Peptide Hormone Families

Insulin Family	Glycoprotein Family	POMC Family
Insulin Insulinlike growth factor I (IGF-1, somatomedin C) Insulinlike growth factor II Relaxin	Lutenizing hormone (LH) Follicle-stimulating hormone (FSH) Thyroid-stimulating hormone (TSH) Chorionic gonadotropin (HCG)	Adrenocorticotropic hormone (ACTH) Melanocyte-stimulating hormone (MSH)

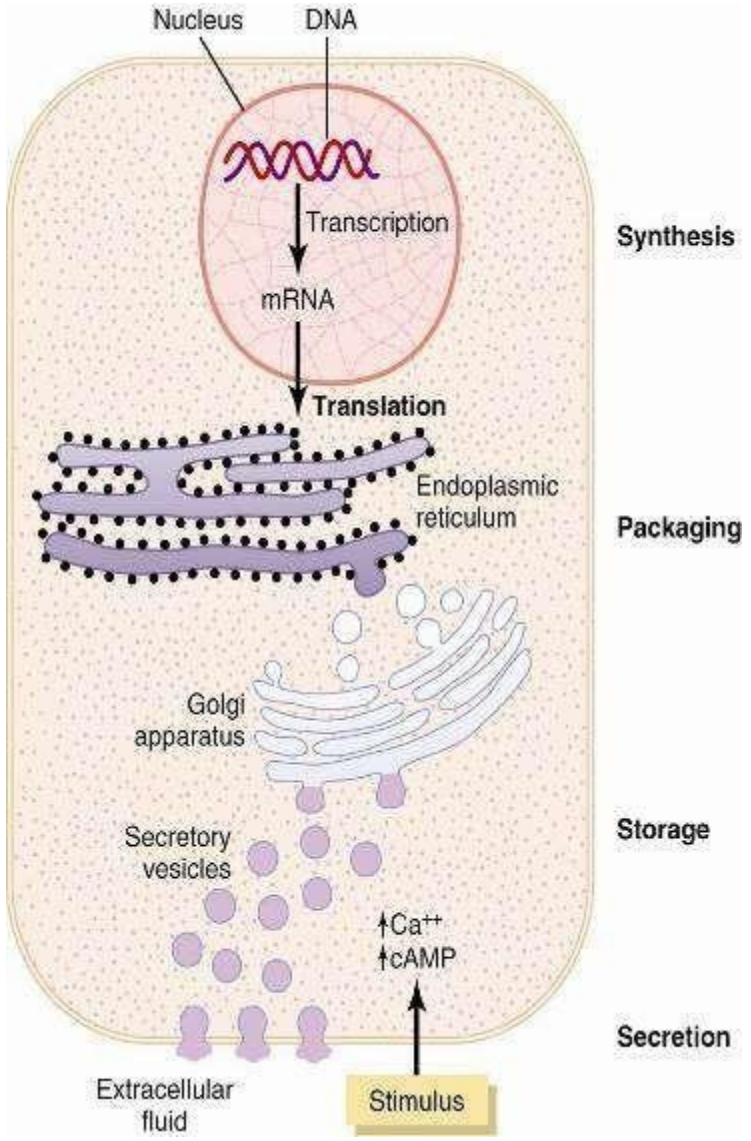
POMC=Pro-opiomelanocorticotropin

The "opio" in POMC reflects that this precursor protein gives rise to opioid peptide, POMC is also related to enkephalins.

Secretin-Glucagon Family	Growth Hormone Family	Neurohypophyseal Family
		From posterior pituitary
Secretin Glucagon Gastrointestinal polypeptide Glicentin Gastric inhibitory polypeptide (GIP) Glucagon-like peptide 1 (GLP-1)	Growth hormone (GH) Prolactin (PRL) Chorionic somatomammotrophin (HCS) or Human placental lactogen (HPL)	Antidiuretic hormone (ADH) Oxytocin

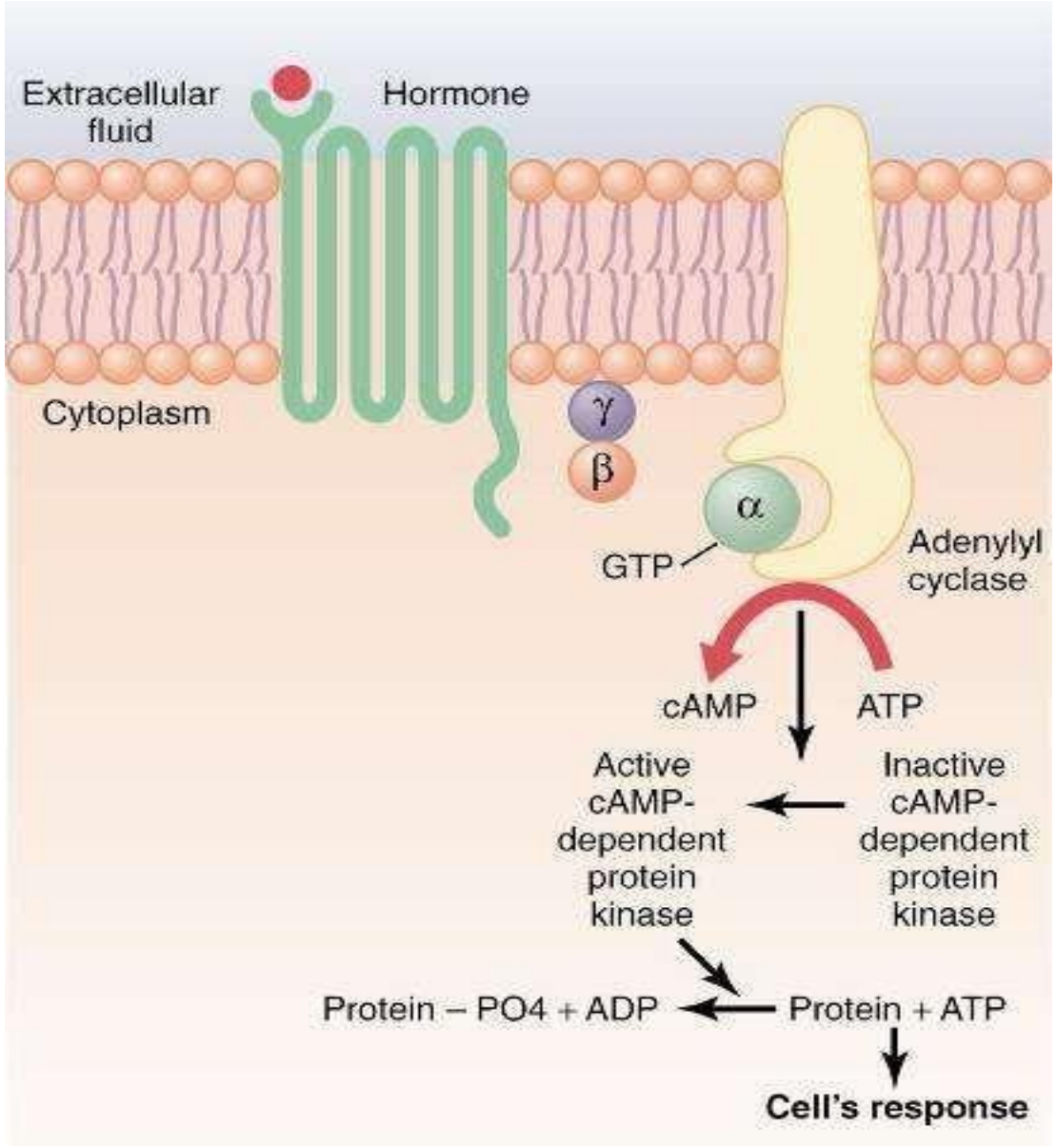
Synthesis & Secretion of Peptide Hormones

- As mentioned before, hormones are synthesized in the form of **prohormones** or **preprohormones**, which are later modified through **post-translational processing**(in golgi to release the hormone inside vesicles). The initial cleavage of the **signal peptide** occurs in the **endoplasmic reticulum**, and further modifications such as packaging and activation often occur in the **Golgi apparatus** and finally these **hormones** gets **released out** of the cells by **exocytosis**.



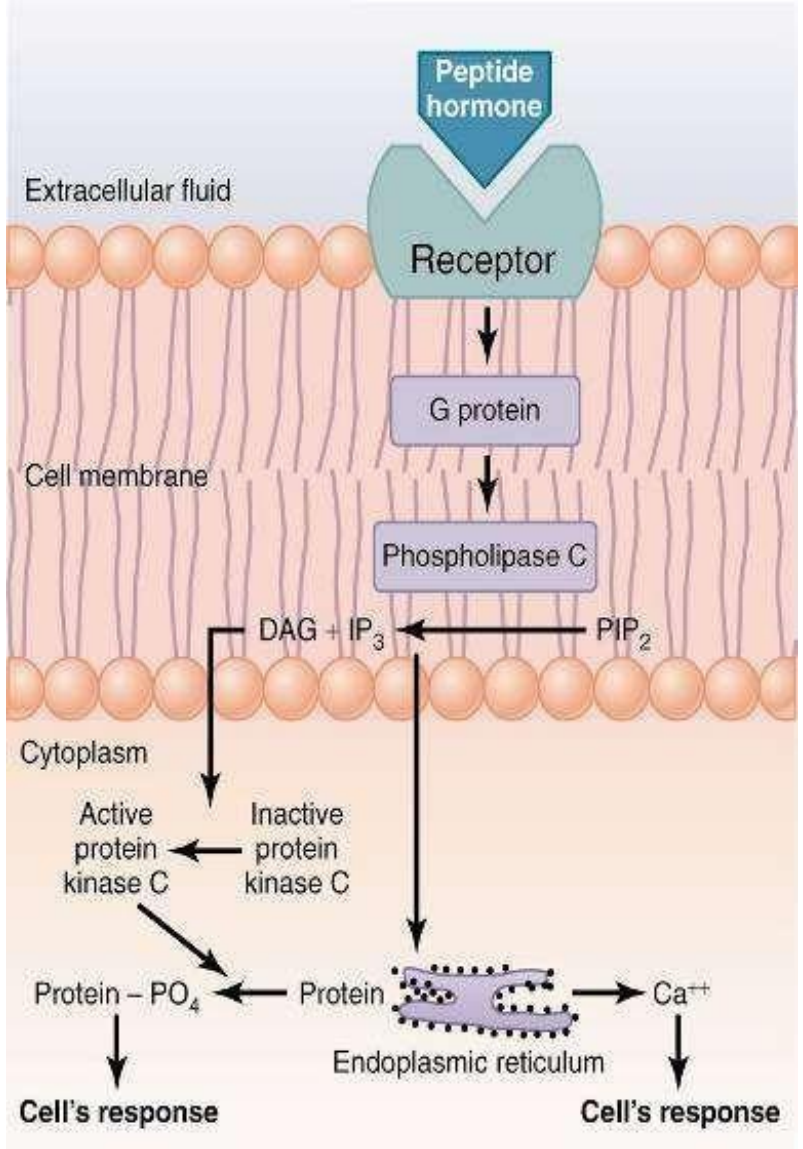
Cyclic Adenosine Monophosphate (cAMP) Second Messenger Mechanism

This slide talks about G protein coupled receptor and cAMP as a second messenger, discussed in detail in slide 21.



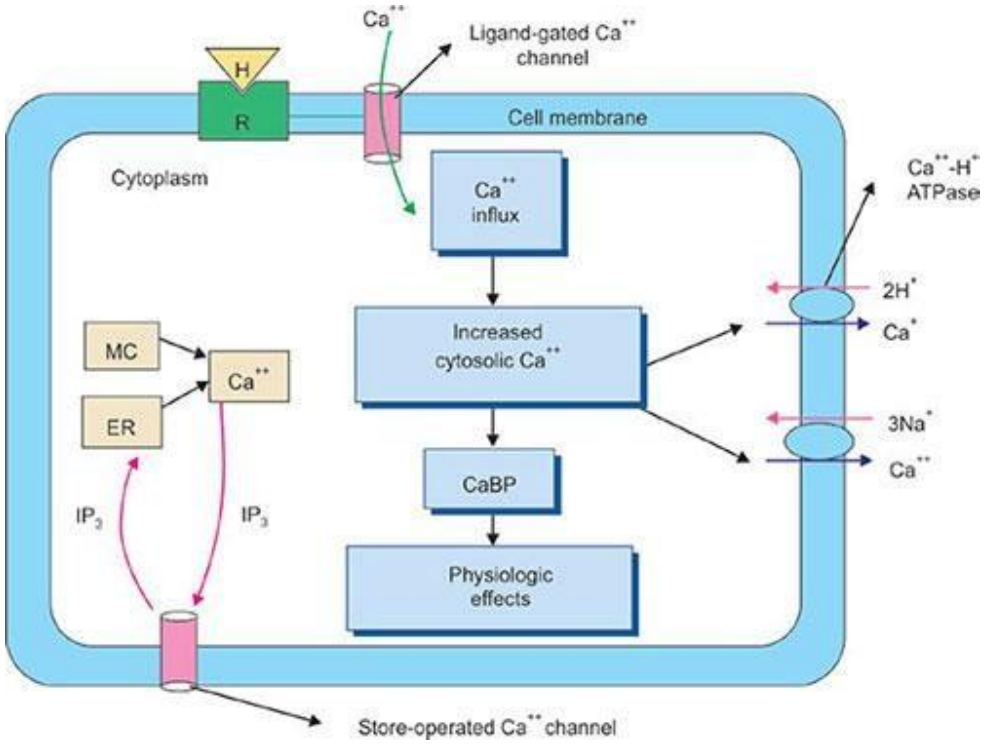
Cell Membrane Phospholipid Second Messenger System

- The hormone stimulates the activation of **phospholipase C**, which leads to the production of **diacylglycerol (DAG)** and **inositol triphosphate (IP_3)**.
- **IP_3** goes to the ER and promotes the release of **calcium ions (Ca^{2+})** from intracellular stores.
- These secondary messengers (**DAG and Ca^{2+}**) activate **Protein Kinase C (PKC)**, which triggers the final cellular response (phosphorylation).



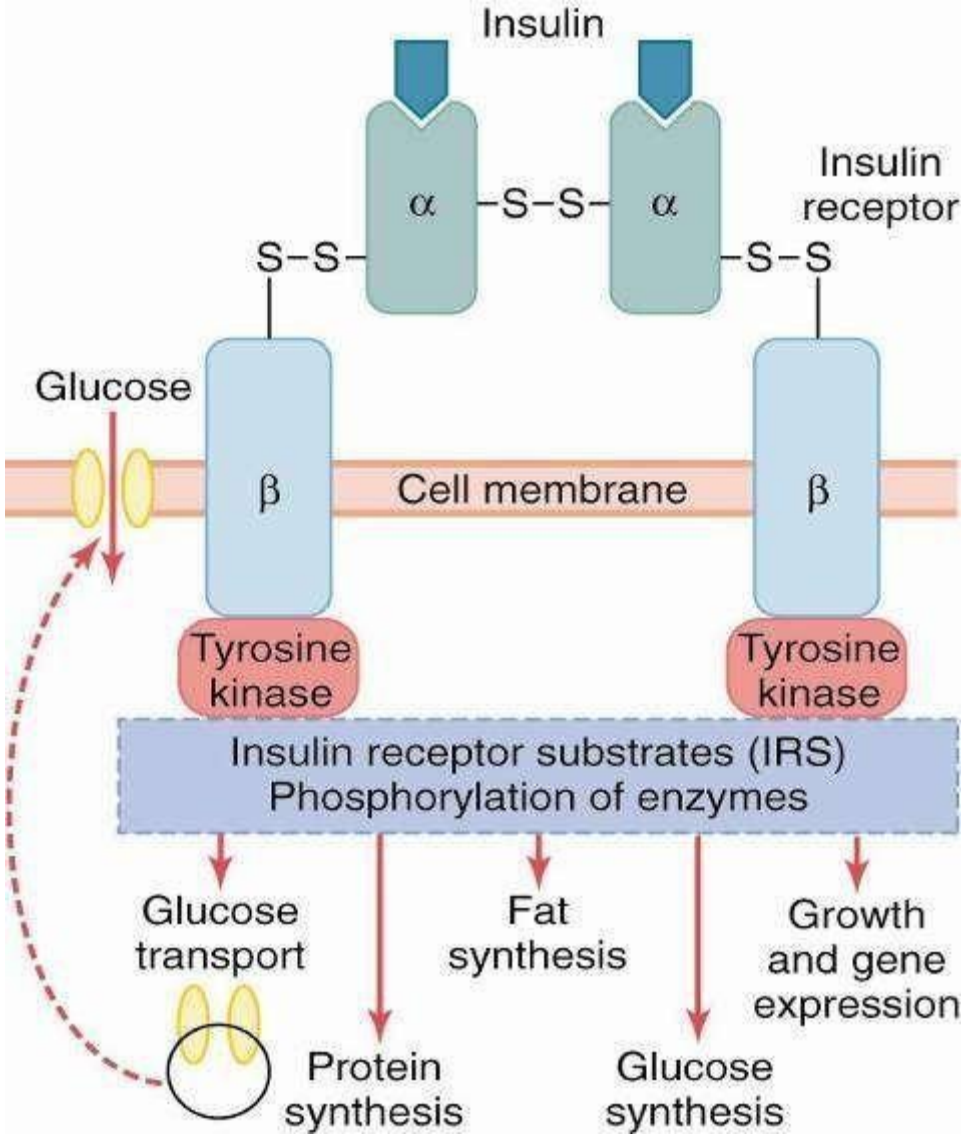
Cell Membrane Phospholipid Second Messenger System

- The hormone stimulates the activation of **phospholipase C**, which leads to the production of **diacylglycerol (DAG)** and **inositol triphosphate (IP_3)**.
- **IP_3** then promotes the release of **calcium ions (Ca^{2+})** from intracellular stores.
- The free Ca^{2+} then binds to **calmodulin**(can bind up to 2–4 calcium molecules), forming a complex that activates **Ca^{2+}/calmodulin-dependent kinases (CaMKs),** these enzymes trigger specific cellular responses such as muscle contraction, secretion, or gene expression.



The Insulin Receptor & Mechanisms of Insulin Action

- The insulin receptor is a **heterotetramer** composed of two extracellular **α-subunits** and two transmembrane **β-subunits**, linked by disulfide bonds, when insulin binds to the α-subunits, it induces a **conformational change** that activates the tyrosine kinase activity of the β-subunits, this leads to **autophosphorylation** of specific tyrosine residues within the intracellular domain. These phosphorylated sites then recruit and activate **insulin receptor substrates (IRS proteins)**, which serve as **docking platforms** for downstream signaling molecules. This cascade activates multiple pathways, resulting in increased **glucose uptake** (e.g., via GLUT4 translocation), enhanced **protein and fat synthesis**, increased **glycogen storage**, and stimulation of **cell growth and gene expression** (new protein synthesis, slowest part of insulin action).



Protein Hormones - Mechanisms of Action

Adenylyl Cyclase Mechanism	Phospholipid Mechanism (DAG+IP3)	Guanylate Cyclase Mechanism	Tyrosine Kinase/ Cytokine Receptor Mechanism
ACTH	GnRH	ANP	Insulin
LH	TRH		IGF-1
FSH	PTH		GH
TSH	Angiotensin II		Prolactin
GHRH	ADH (V_1 receptor)		
Somatostatin	Oxytocin		
ADH (V_2 receptor)			
HCG			
MSH			
CRH			
Calcitonin			
PTH			
Glucagon			

- ADH (vasopressin) has **two main receptors:**
- **V1 receptor**, which is found on **vascular smooth muscle** and causes **vasoconstriction.**
- **V2 receptor**, which is found in the **renal tubules** and **stimulates water reabsorption.**

DO NOT MEMORIZE

Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

Hormone	Protein binding (%)	Plasma half-life	Metabolic clearance (ml/minute)
Thyroid			
Thyroxine (Lipid soluble)	99.97	6 days	0.7
Triiodothyronine	99.7	1 day	18
Steroids			
Cortisol	94	100 min	140
Testosterone	89	85 min	860
Aldosterone	15	25 min	1100
Proteins			
Thyrotropin	little	50 min	50
Insulin	little	8 min	800
Antidiuretic hormone	little	8 min	600

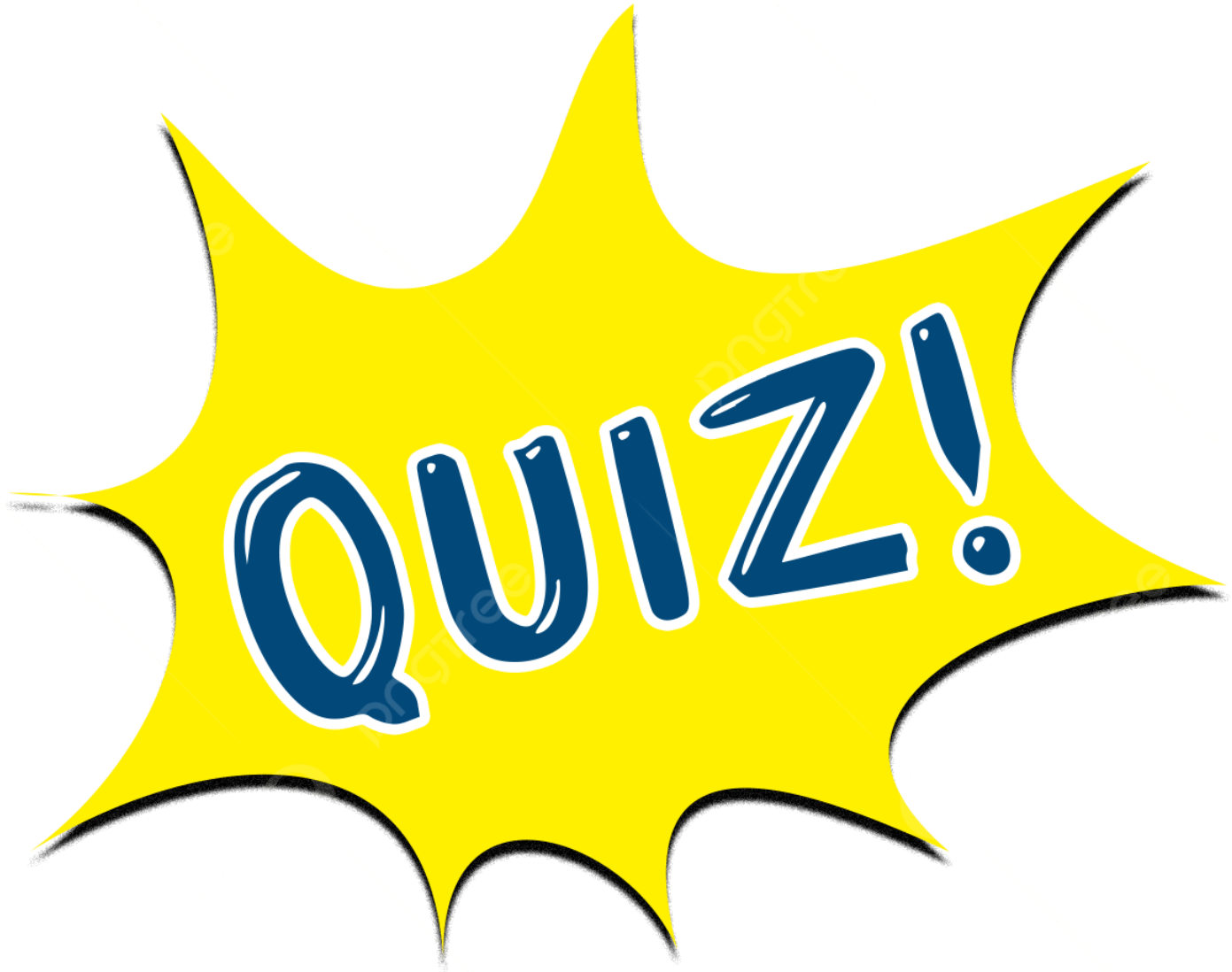
MCR = (mg/minute removed) / (mg/ml of plasma) = ml cleared/minute

Do not memorize the numbers, further explanation in the next slide

Correlation of Plasma Half-Life & Metabolic Clearance of Hormones with Degree of Protein Binding

- The more **lipophilic** a hormone is, the less it dissolves in plasma, so it binds extensively to **transport proteins** for solubility and stable circulation. These **hormone-transporter complexes** are relatively large and are **not excreted unless the hormone is unbound**, causing their **elimination rate to be lower** and their **half-life to be longer**.

- Water-soluble hormones dissolve freely in plasma and do not require transport proteins. Because they circulate unbound, they are **readily available for excretion**, resulting in a **higher elimination rate** and a **shorter half-life**.


QUIZ!

Classes of Hormones

- Peptide & Protein Hormones
- **Steroid Hormones**
- Amine Hormones

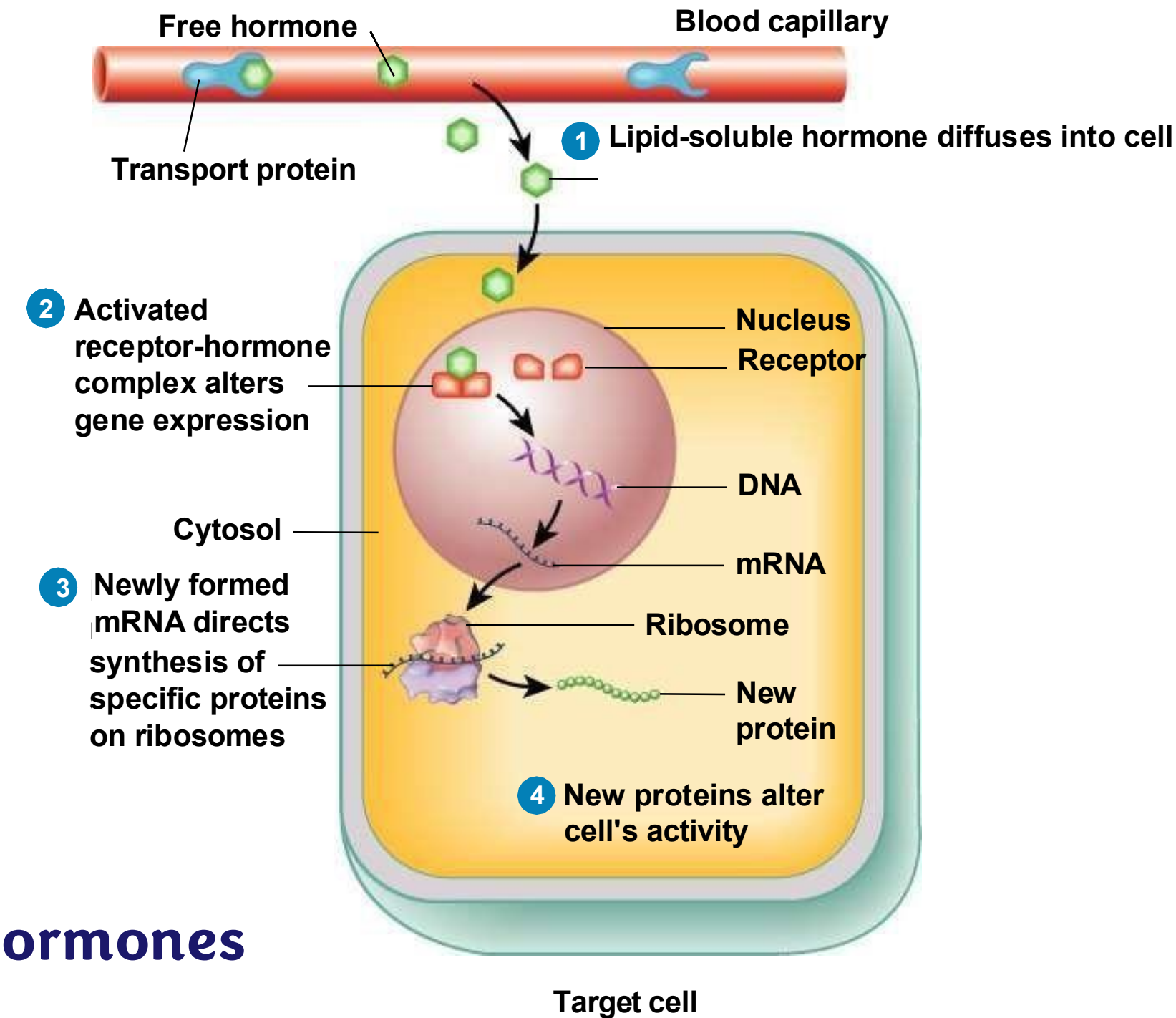
Steroid hormones are a class of lipid-soluble hormones derived from cholesterol

Steroid Hormones

Gland/Tissue	Hormones
Adrenal Cortex	Cortisol =glucocorticoid =regulation of glucose metabolism (carbohydrate)
	Aldosterone =mineralocorticoid =controlling (Na^+) and (K^+) balance
	Androgens =sex hormone
Testes	Testosterone =male sex hormone
Ovaries	Estrogens, Progesterone steroids
Corpus Luteum*	Estrogens, Progesterone
Placenta	Estrogens, Progesterone
Kidney	1,25-Dihydroxycholecalciferol The kidney converts inactive Vitamin D (25-hydroxycholecalciferol) into its active form (1,25-hydroxycholecalciferol) in response to the parathyroid hormone (PTH)

The corpus luteum (yellow body) is a temporary endocrine gland formed **in the ovary after ovulation from the remains of the ruptured follicle*

Lipid-soluble Hormones



Lipid-soluble Hormones / Mechanism of Action

(1) Lipid-soluble hormones follow a specific mechanism of action due to their chemical nature. Since they are **not water-soluble,** they must be transported in the bloodstream bound to **carrier proteins**. Upon reaching their target cell, the hormone dissociates from the carrier and **diffuses through the cell membrane.**

(2) Inside the cell, the hormone binds to its specific intracellular receptor, which may be located in the **cytoplasm** or the **nucleus**. The **hormone-receptor complex** then enters the nucleus (if not already there) and binds to a specific DNA sequence known as the **hormone response element (HRE).**

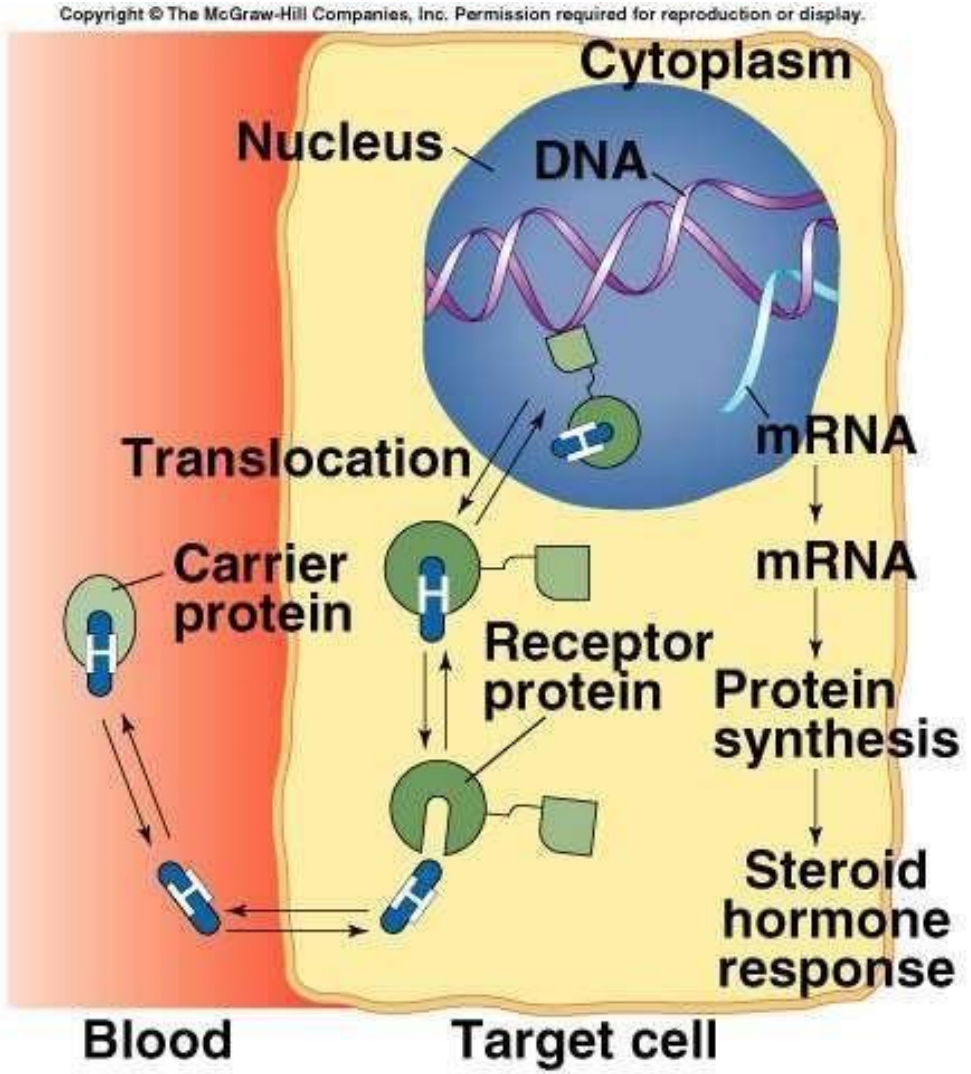
(3,4) This binding initiates **transcription**, producing messenger RNA (mRNA), which then exits the nucleus and is translated into a new protein at the **ribosome**. The resulting protein could be a *receptor, enzyme, ion channel, or other functional molecule.*

Because this mechanism involves transcription and translation, it tends to have a slow onset but long-lasting effects.

Hormones That Bind to Nuclear Receptor Proteins

- Lipophilic steroid and thyroid hormones are attached to plasma carrier proteins.
- Hormones dissociate from carrier proteins to pass through lipid component of the target plasma membrane.
- Receptors for the lipophilic hormones are known as **nuclear hormone receptors**.

(See next slide)



Nuclear Hormone Receptors

- Steroid receptors are located in cytoplasm and in the nucleus.
- Function within cell to **activate genetic transcription**.
  - Messenger RNA directs synthesis of specific enzyme proteins that change metabolism.
- Each nuclear hormone receptor has 2 regions (dimer):
  - A ligand (hormone)-binding domain.
  - DNA-binding domain.
- Receptor must be activated by binding to hormone before binding to specific region of DNA called HRE (hormone responsive element).
  - Located adjacent to gene that will be transcribed.

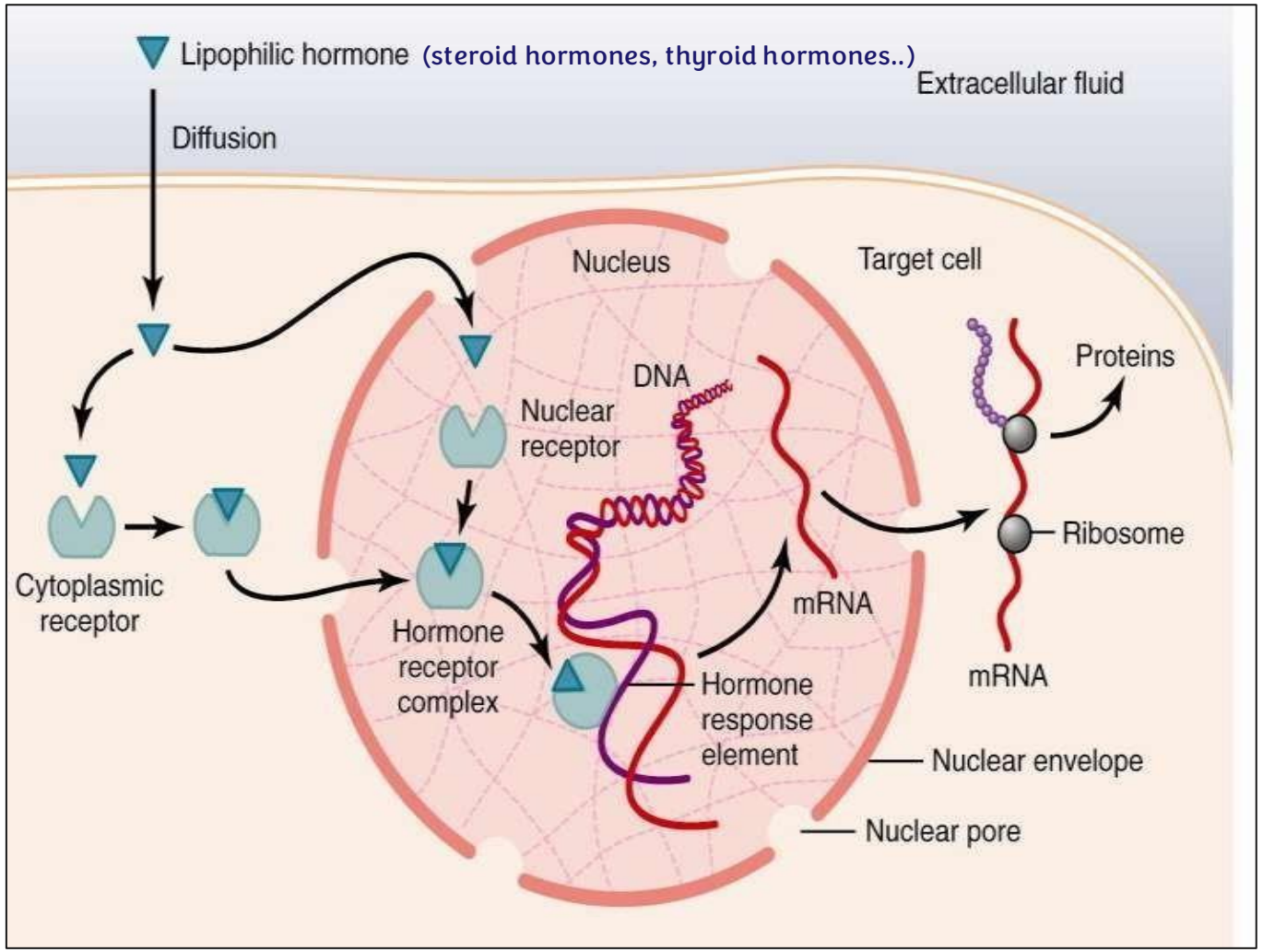
Steroid & Thyroid Hormones - Mechanism of Action

The same mechanism ☺☺☺

Nuclear hormone receptors function as dimers and have two main parts:

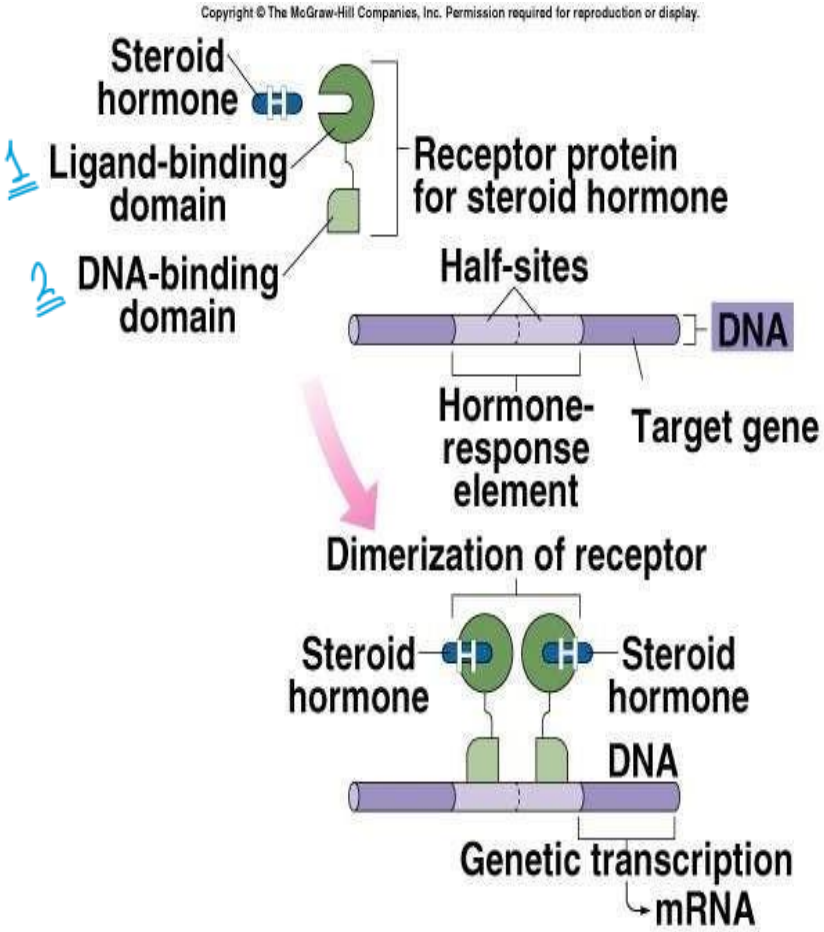
- **A hormone-binding domain** (binds the hormone to activate the receptor)
- **A DNA-binding domain** (binds to a specific DNA region)

Once activated by the hormone, the receptor binds to the hormone response element (HRE) on DNA, which is located near the target gene, to initiate transcription and protein synthesis



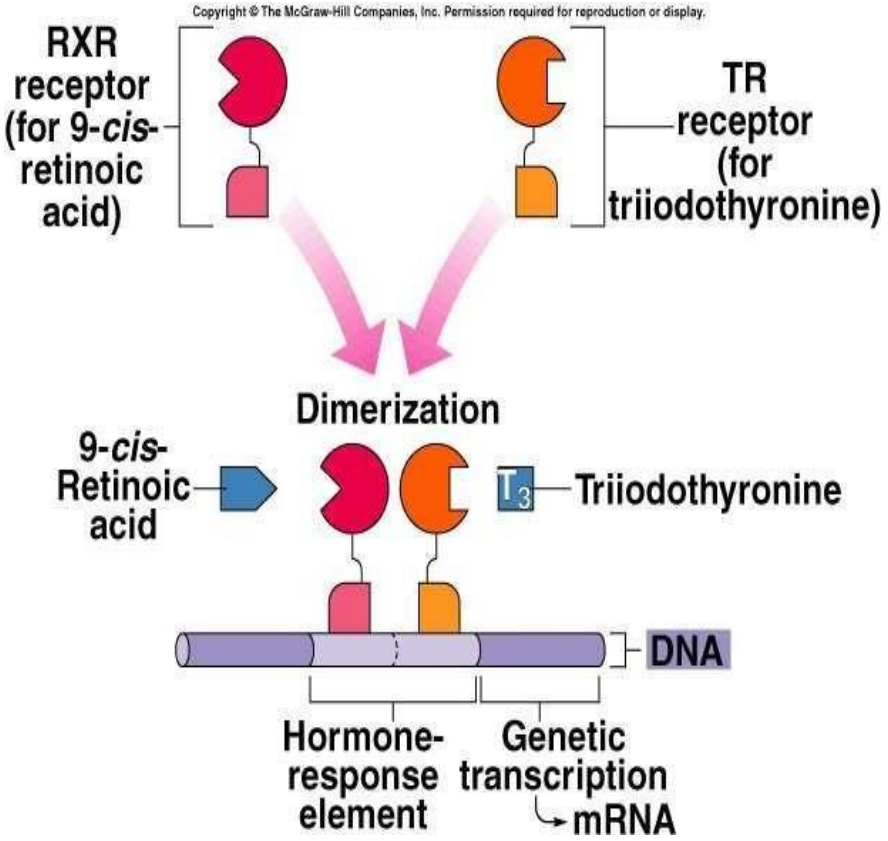
Mechanisms of Steroid Hormone Action

- Cytoplasmic receptor binds to steroid hormone.
- Translocates to nucleus.
- DNA-binding domain binds to specific HRE of the DNA.
- Dimerization occurs.
  - Process of 2 receptor units coming together at the 2 half-sites.
- Stimulates transcription of particular genes.



Mechanism of Thyroid Hormone Action

- **T_4** passes into cytoplasm and is **converted to T_3**.
- Receptor proteins **located in nucleus**.
  - T_3 binds to ligand-binding domain.
  - Other half-site is vitamin A derivative (9-cis-retinoic) acid.
  - DNA-binding domain can then bind to the half-site of the HRE.
  - Two partners can bind to the DNA to activate HRE.
    Stimulate transcription of genes.



- The receptor forms a dimer, with one part binding to the **thyroid hormone (primarily T3 (more active form), or less commonly T4)**, and the other part binding to **a vitamin A derivative known as 9-cis-retinoic acid**
- The resulting gene transcription leads to the formation of new proteins, which may include **growth-related proteins**

Physiological Effects of Thyroid Hormones

Growth and CNS Development

T3 and T4 are critical for normal growth and brain development, especially in the fetal period and the first two years after birth. During fetal development, the fetus receives T3 and T4 from both its own thyroid and the mother's thyroid via the placenta. If a newborn has congenital hypothyroidism, it may result in neurodevelopmental deficits unless treated early.

Cardiovascular System

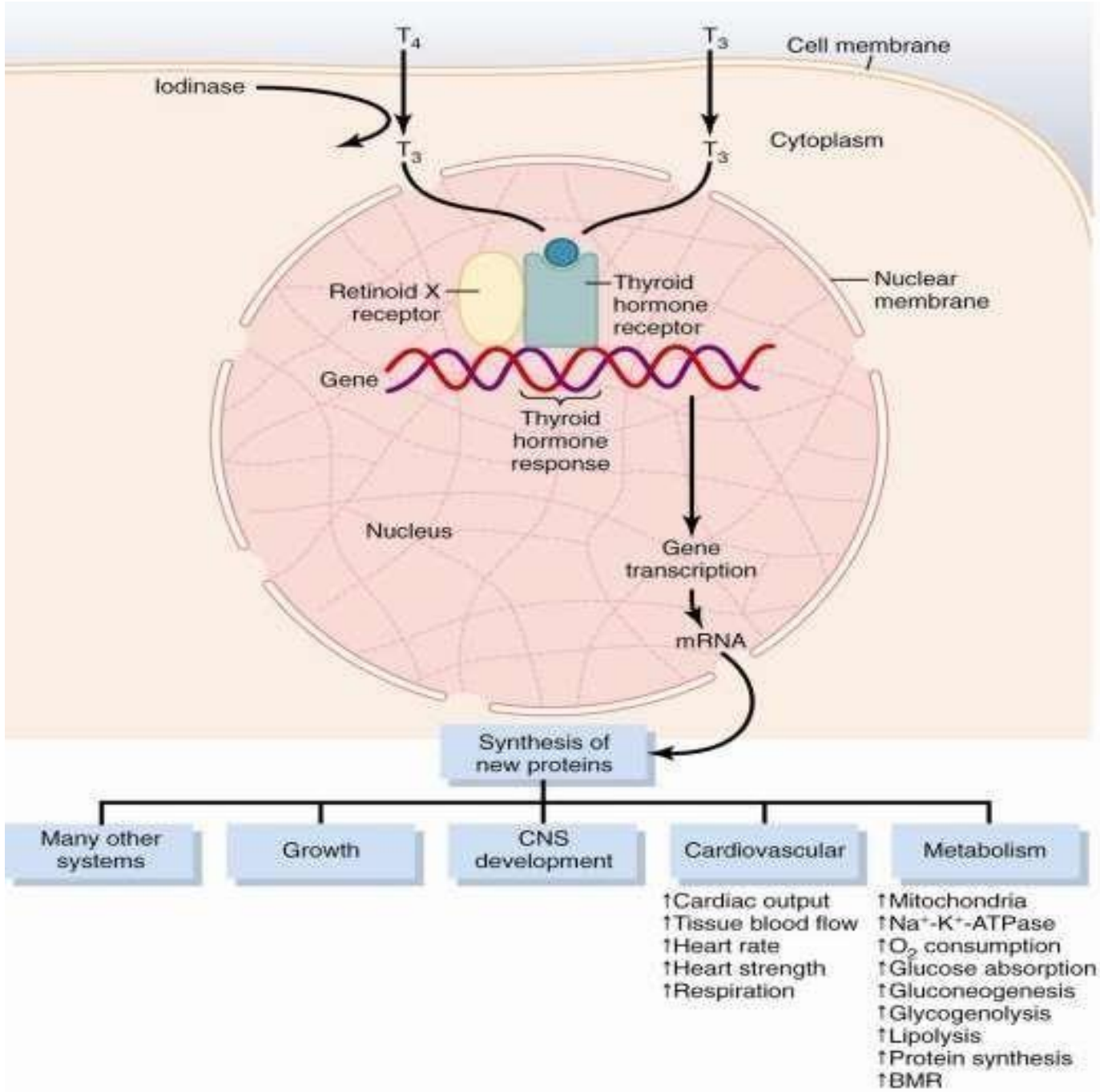
- Increases cardiac output.
- Increases heart rate and **myocardial contractility** (force of heart contractions).
- Enhances respiratory rate to meet increased oxygen demand.
- Upregulates β-adrenergic receptors and other proteins (as a result of transcription and translation)

Metabolic Regulation

- Increases both the number and size of mitochondria, enhancing cellular energy production.
- Stimulates Na^+/K^+ ATPase activity, increasing oxygen consumption and ATP usage, which leads to heat production
- Increases:
  - Glucose absorption from the gut.
  - Gluconeogenesis – production of glucose from non-carbohydrate sources.
  - Glycogenolysis – breakdown of glycogen to glucose.
  - Lipolysis – breakdown of fat stores to free fatty acids.
  - Protein synthesis – especially enzymes involved in metabolic pathways.

Overall effect: Increase in **Basal Metabolic Rate (BMR)**

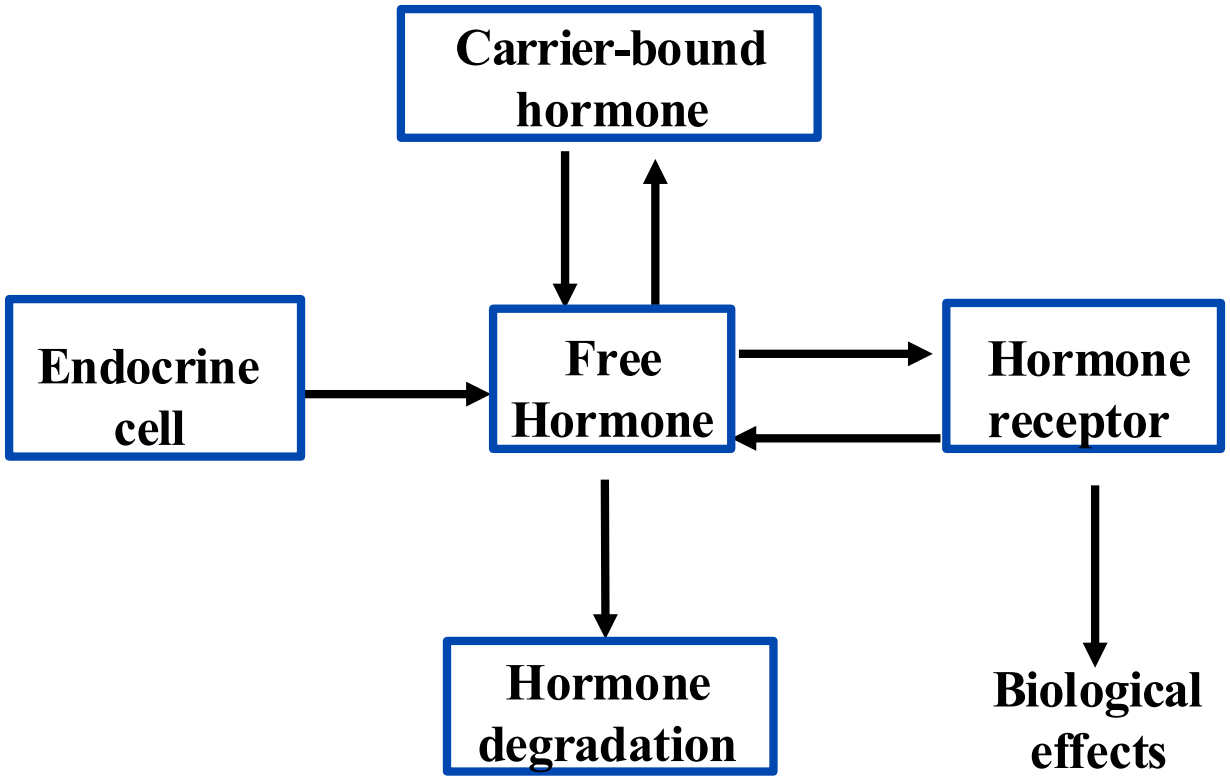
We will discuss the action of thyroid hormones later in more details. However, here's an overview


T_4
T_3
Cell membrane
Iodinase
Cytoplasm
T_3
T_3
Retinoid X receptor
Thyroid hormone receptor
Nuclear membrane
Gene
Thyroid hormone response
Nucleus
Gene transcription
mRNA
Synthesis of new proteins
Many other systems
Growth
CNS development
Cardiovascular
Metabolism
↑Cardiac output
↑Tissue blood flow
↑Heart rate
↑Heart strength
↑Respiration
↑Mitochondria
↑Na^+-K^+-ATPase
↑O_2 consumption
↑Glucose absorption
↑Gluconeogenesis
↑Glycogenolysis
↑Lipolysis
↑Protein synthesis
↑BMR

Circulating Transport Proteins

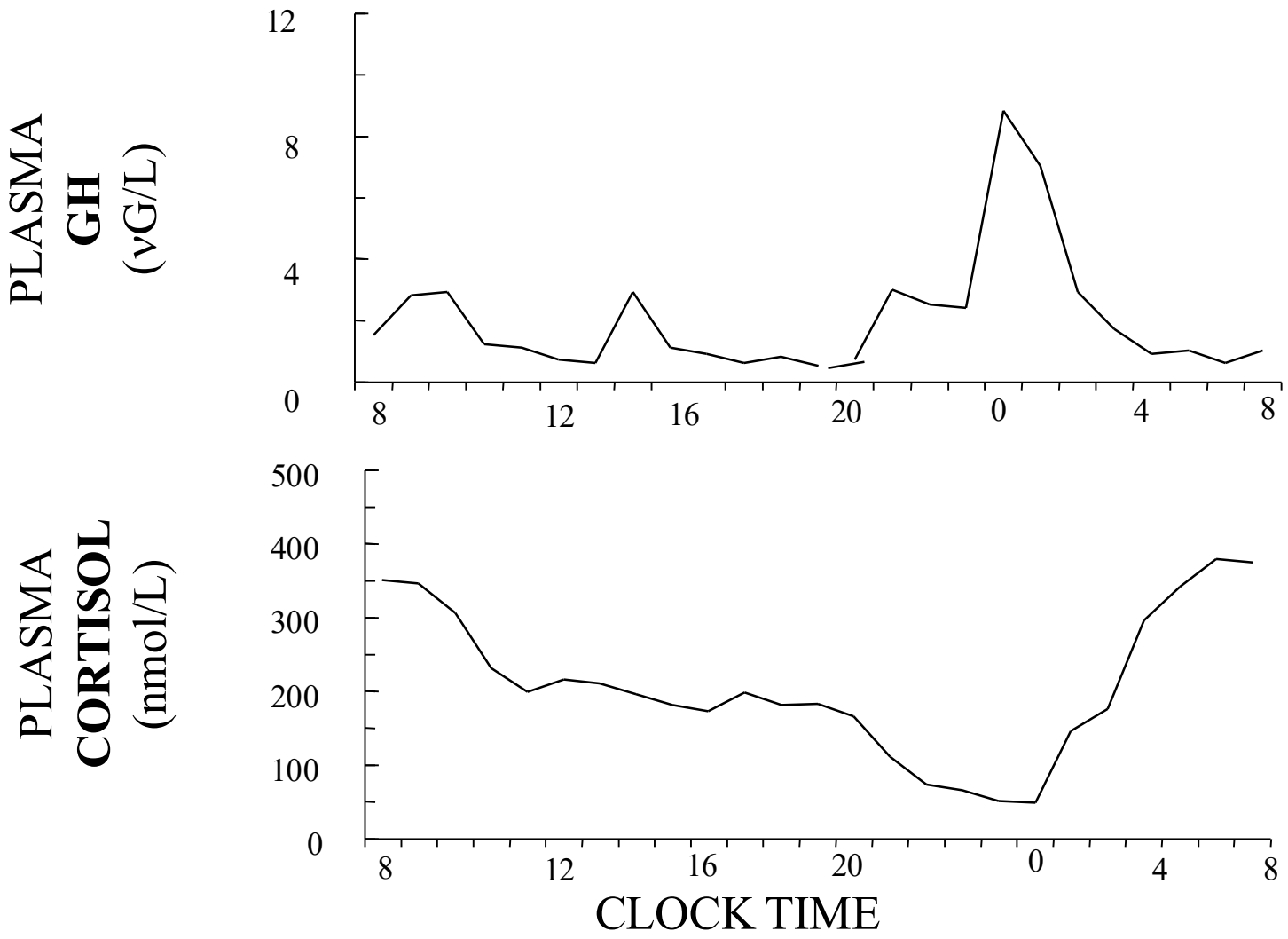
Transport protein		Principles Hormone Transported
Specific	Corticosteroid binding globulin (CBG, transcortin)	Cortisol, aldosterone
	Thyroxine binding globulin (TBG)	Thyroxine, triiodothyronine
	Sex hormone-binding globulin (SHBG)	Testosterone, estrogen
Non-Specific = can bind and carry a variety of molecules, without being selective	Albumin	Most steroids, thyroxine, triiodothyronine
	Transthyretin (prealbumin)	Thyroxine, some steroids

Determinants of Free Hormone Receptor Binding



Endocrine cells secrete hormones in their free form. If the hormone is lipid-soluble, it binds reversibly to a carrier protein in the blood. In contrast, water-soluble hormones do not require carriers; they bind directly to cell surface receptors to exert their biological effects. Eventually, these hormones are subject to metabolism or degradation to terminate their action

Hormonal Rhythms



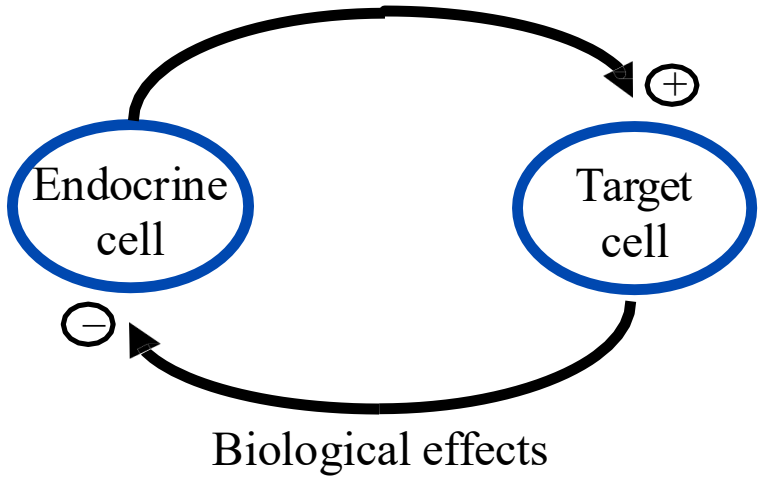
Many hormones are typically not secreted all at once; rather, they are released in a cyclical pattern known as a **pulsatile manner**

Some hormones follow a diurnal (daily) rhythm, with secretion varying at different times of the day

- For example – as you can see–, growth hormone is primarily secreted during the late night hours, especially during deep sleep
- In contrast, hormones like ACTH and cortisol have peak levels in the early morning, aligning with waking and daylight exposure

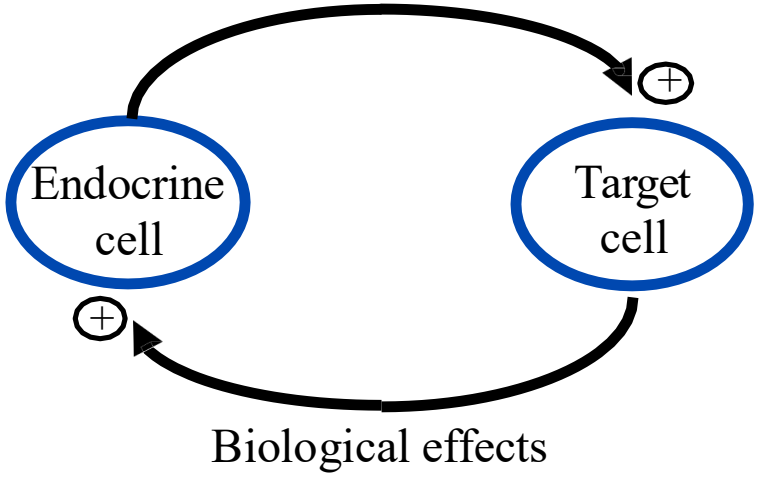
Feedback Mechanisms

Negative Feedback



In negative feedback, when the hormone reaches the target cells and produces a biological effect, or when hormone levels become elevated, this signal is sent back to the endocrine gland to inhibit further secretion. This helps maintain homeostasis

Positive Feedback



In positive feedback, the biological effect from the target cells actually stimulates the endocrine gland to increase hormone secretion, amplifying the response. While most hormonal regulation follows negative feedback, some are regulated by PFM

Endocrine disorders may involve abnormalities in the function of hormone-producing glands. These can be classified into three categories:

- Normal endocrine function.
- Hyperfunction – excessive hormone secretion.
- Hypofunction – insufficient hormone secretion.

✓ In **hyperfunction**, treatment typically involves reducing or blocking hormone production.
✓ In **hypofunction**, hormone replacement therapy is used to restore normal levels.

Causes of Endocrine Hyperfunction

Neoplastic	**Benign**: pituitary adenomas, hyperparathyroidism, autonomous thyroid or adrenal nodules
	Malignant: adrenal and thyroid cancer
	Ectopic (hormone production that occurs outside its normal site) : ACTH (adrenocorticotropic hormone) , SIADH (ADH is secreted from non-pituitary sources)
Autoimmune	Graves' disease (An autoimmune disorder causing hyperthyroidism due to overstimulation of the thyroid gland)
Iatrogenic (doctor-induced)	Cushing's syndrome (excessive corticosteroid administration)
	Hypoglycemia (excess insulin intake)
Infectious/Inflammatory	Subacute thyroiditis
Activating receptor mutations	TSH

Hormone Activity

- Hormones affect only specific target tissues with specific receptors
- Receptors are dynamic and constantly synthesized and broken down
  - Down-regulation: A decrease in the number of receptor sites on a cell, leading to reduced responsiveness to a ligand (↓action)
  - Up-regulation: An increase in the number of receptor sites on a cell, leading to increased sensitivity to a ligand (↑action)

Effects of [Hormone] on Tissue Response

- Priming effect (upregulation):
  - Increase number of receptors formed on target cells in response to particular hormone.
  - Greater response by the target cell.

Some hormones are required to act first before other hormones can exert their full effect—this is known as the priming effect. For example, estrogen increases the number of progesterone receptors, enhancing the response to progesterone

- Desensitization (downregulation):
  - Prolonged exposure to high [polypeptide hormone].
    - Subsequent exposure to the same [hormone] produces less response.
      - Decrease in number of receptors on target cells.
        - Insulin in adipose cells.
  - Pulsatile secretion (which does not occur in all hormones) may prevent downregulation.

Prolonged exposure to a hormone can cause downregulation of its receptors, often by internalizing them into the cell. As a result, the hormone's effect is reduced over time despite its continued presence

Effects of [Hormone] on Tissue Response

- [Hormone] in blood reflects the rate of secretion.
- Half-life:
  - Time required for the blood [hormone] to be reduced to ½ reference level.
    - Minutes (like insulin hormone) to days (like thyroid hormone).
- Normal tissue responses are produced only when [hormone] are present within physiological range.
- Varying [hormone] within normal, physiological range can affect the responsiveness of target cells.

Locations of hormone receptors in target cells

This diagram illustrates the various locations of hormone receptors in target cells:

On the cell membrane, receptors are used by many peptide hormones, growth factors, and amino acid-derived hormones Such as catecholamines. These hormones are not lipid-soluble, so they cannot cross the membrane and must bind to surface receptors

- **In the cytoplasm, receptors bind to specific steroid hormones like glucocorticoids in their inactive (unliganded) form.** Once the hormone binds, the receptor-hormone complex moves into the nucleus to influence gene expression

- **Within the nucleus, receptors are already located inside and directly bind to other steroid hormones or thyroid hormones,** allowing them to regulate gene transcription directly upon hormone entry into the cell

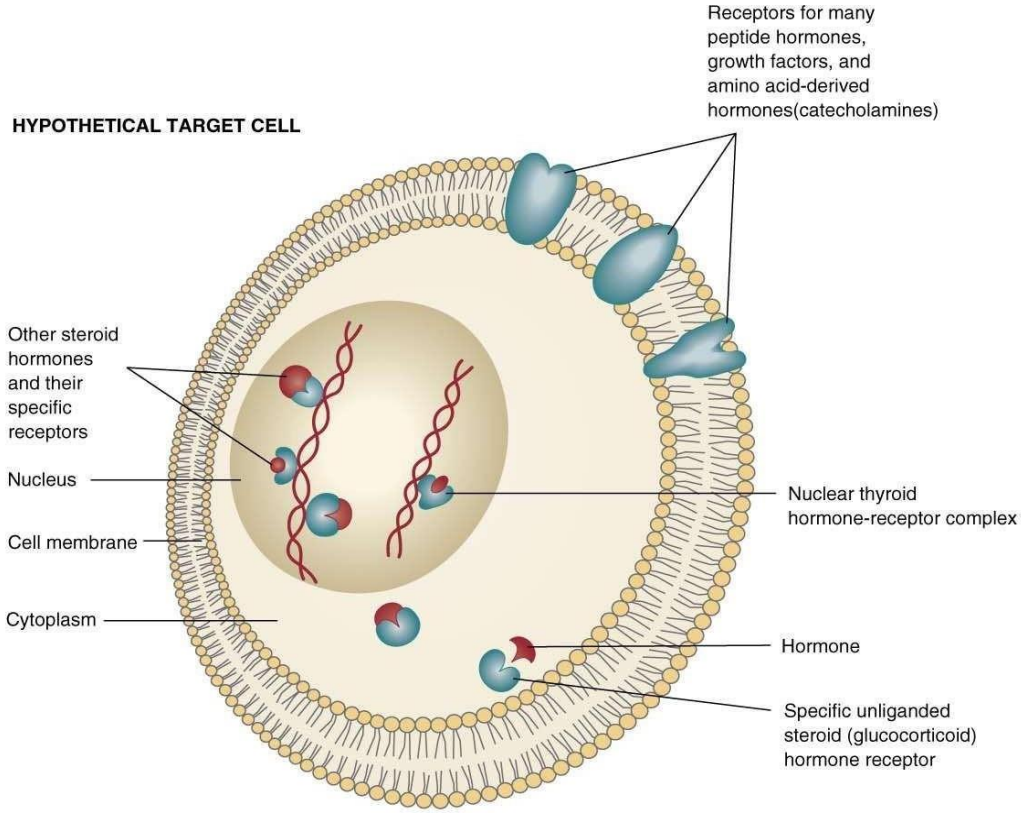
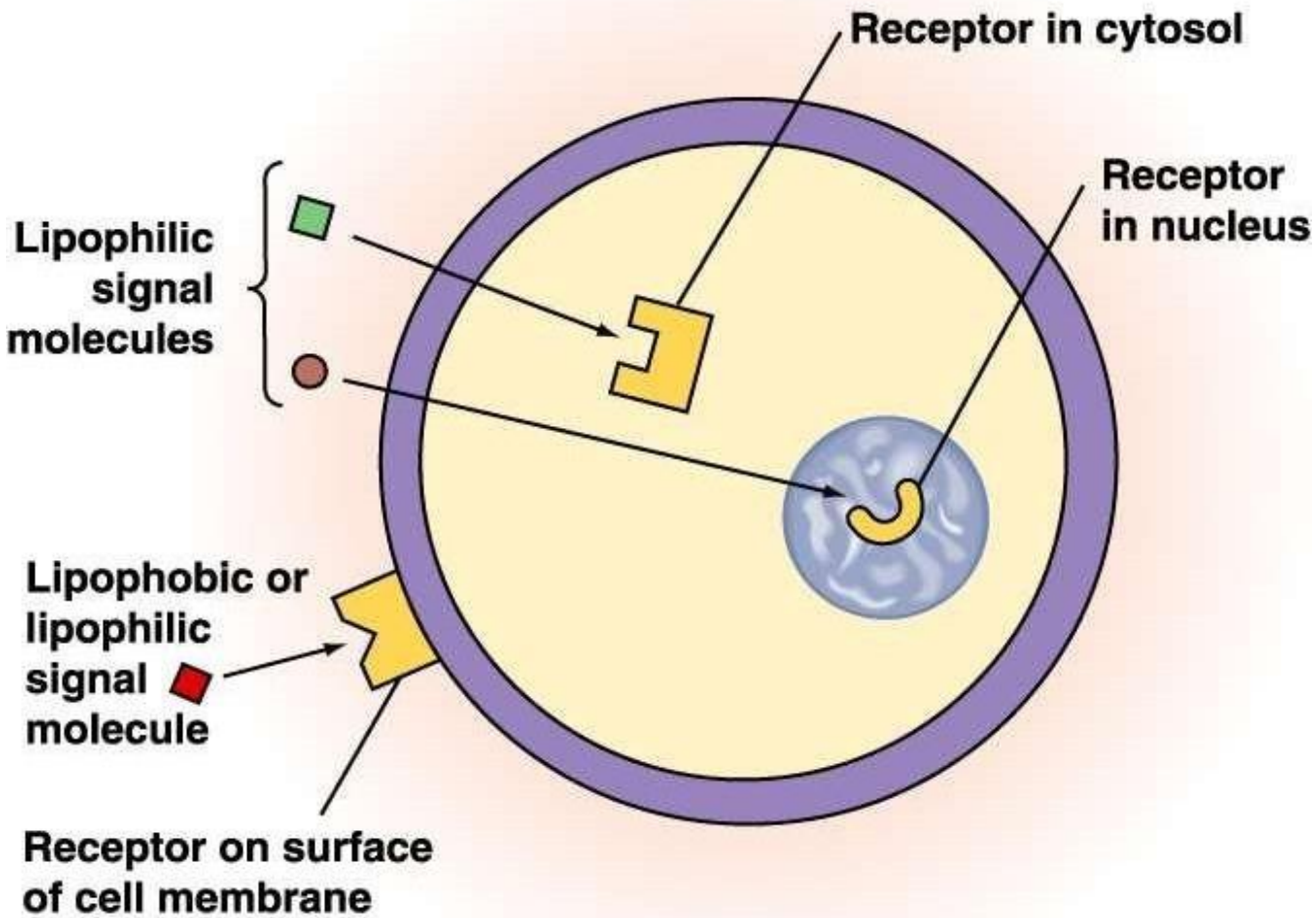


Figure 23.1. Diagram showing the different locations of classes of hormone receptors expressed by a target cell.



Lipophilic hormones cross the cell membrane and bind to receptors in the cytoplasm or nucleus, while hydrophilic (water-soluble) hormones bind to receptors on the cell surface.

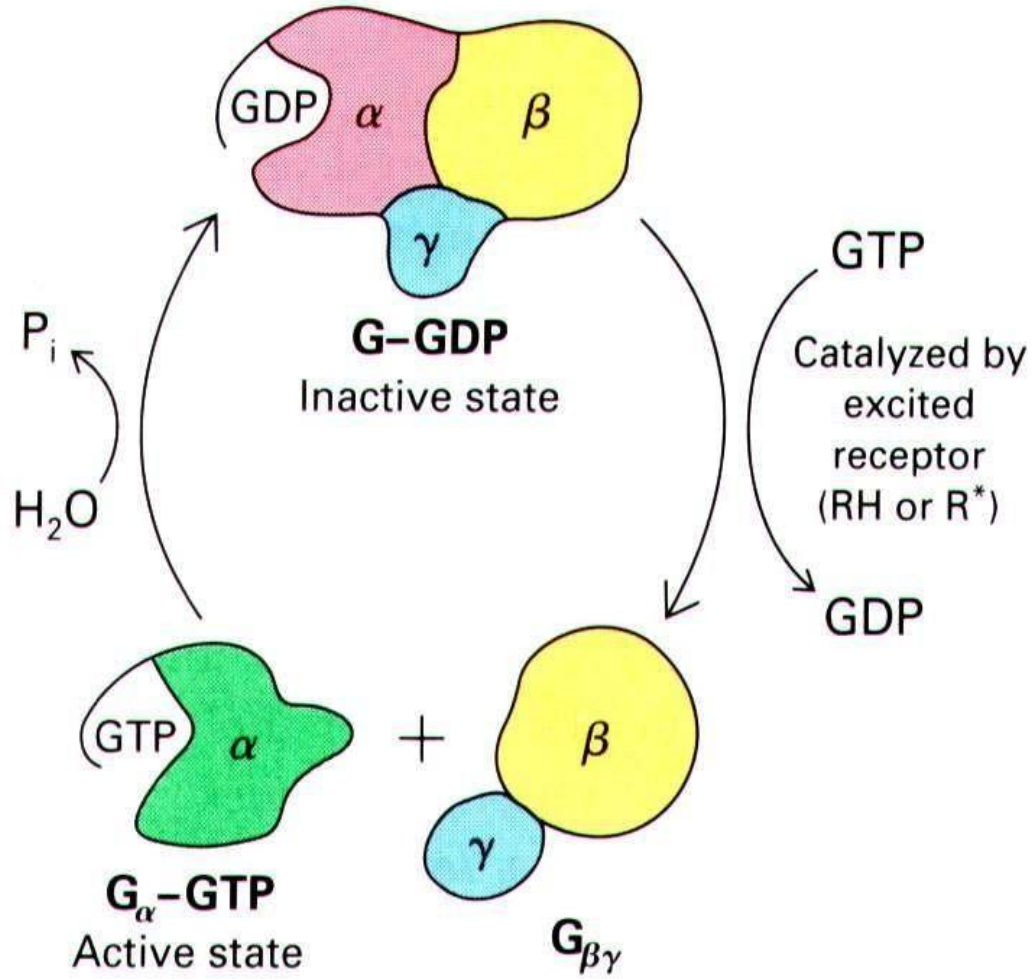
Mechanisms of Hormone Action

- Hormones of same chemical class have similar mechanisms of action.
  - Similarities include:
    - Location of cellular receptor proteins depends on the chemical nature of the hormone (inside or on the surface).
    - Events that occur in the target cells (second messager, protein synthesis,..)
- To respond to a hormone:
  - Target cell must have specific receptors for that hormone (specificity).
    - Hormones exhibit:
      - Affinity*: The strength of the binding between a hormone (or ligand) and its receptor (bind to receptors with high bond strength).
      - Saturation: The point at which all available receptors are occupied by the hormone (low capacity of receptors).

*Km (Michaelis constant) is the substrate concentration at which an enzyme works at half its maximum speed (Vmax) Low Km → high affinity (enzyme binds substrate tightly) VS. High Km → low affinity (enzyme binds substrate weakly)

Mechanisms of Hormone Action

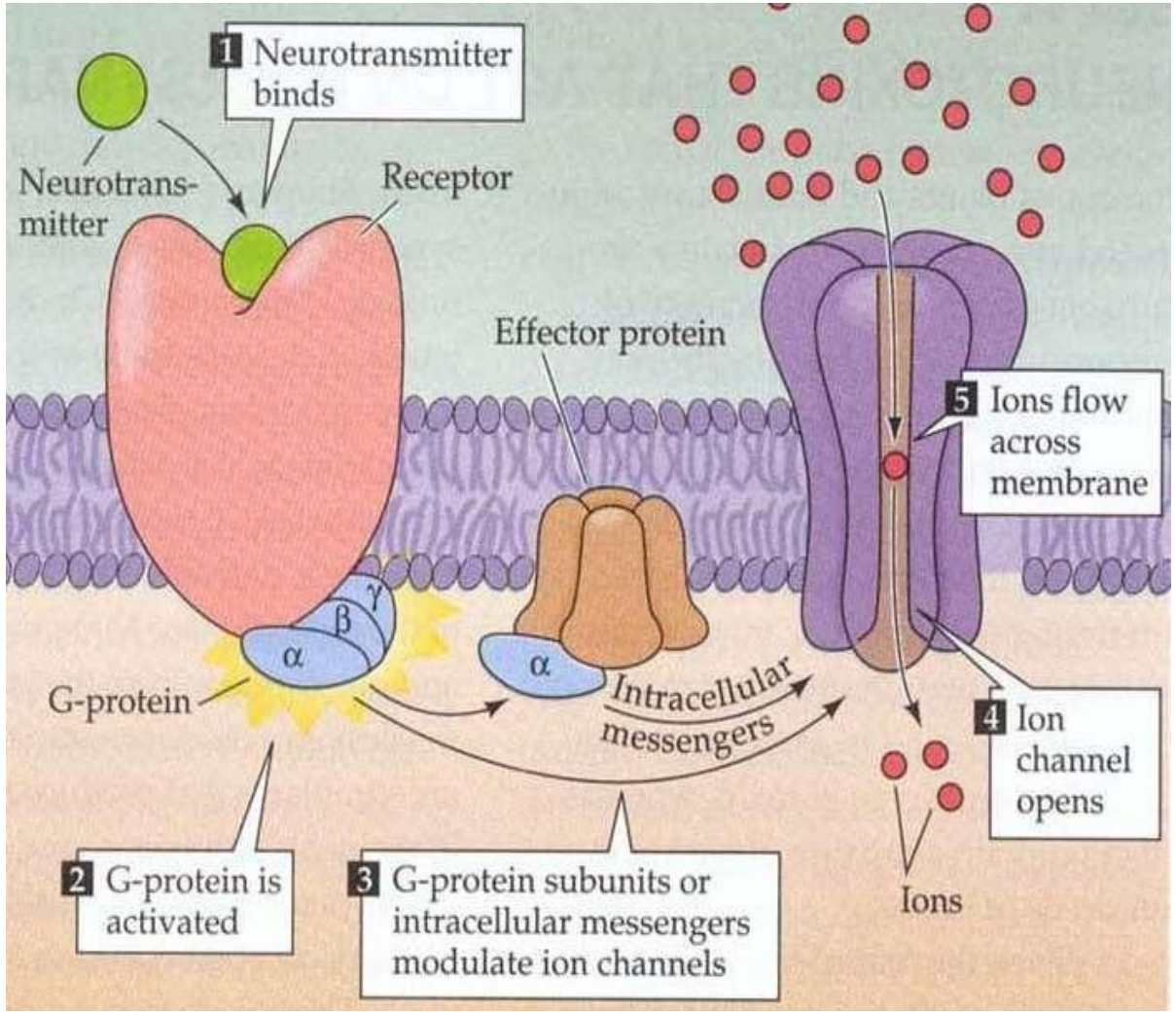
- Response depends on both hormone and target cell
  - Lipid-soluble hormones bind to receptors inside target cells
  - Water-soluble hormones bind to receptors on the plasma membrane
    - Activates second messenger system
    - Amplification of original small signal (activation of 1 G protein → activates adenylyl cyclase → produces many cAMP molecules → activates many protein kinases → phosphorylate hundreds of target proteins)
- Responsiveness of target cell depends on
  - Hormone's concentration
  - Abundance of target cell receptors



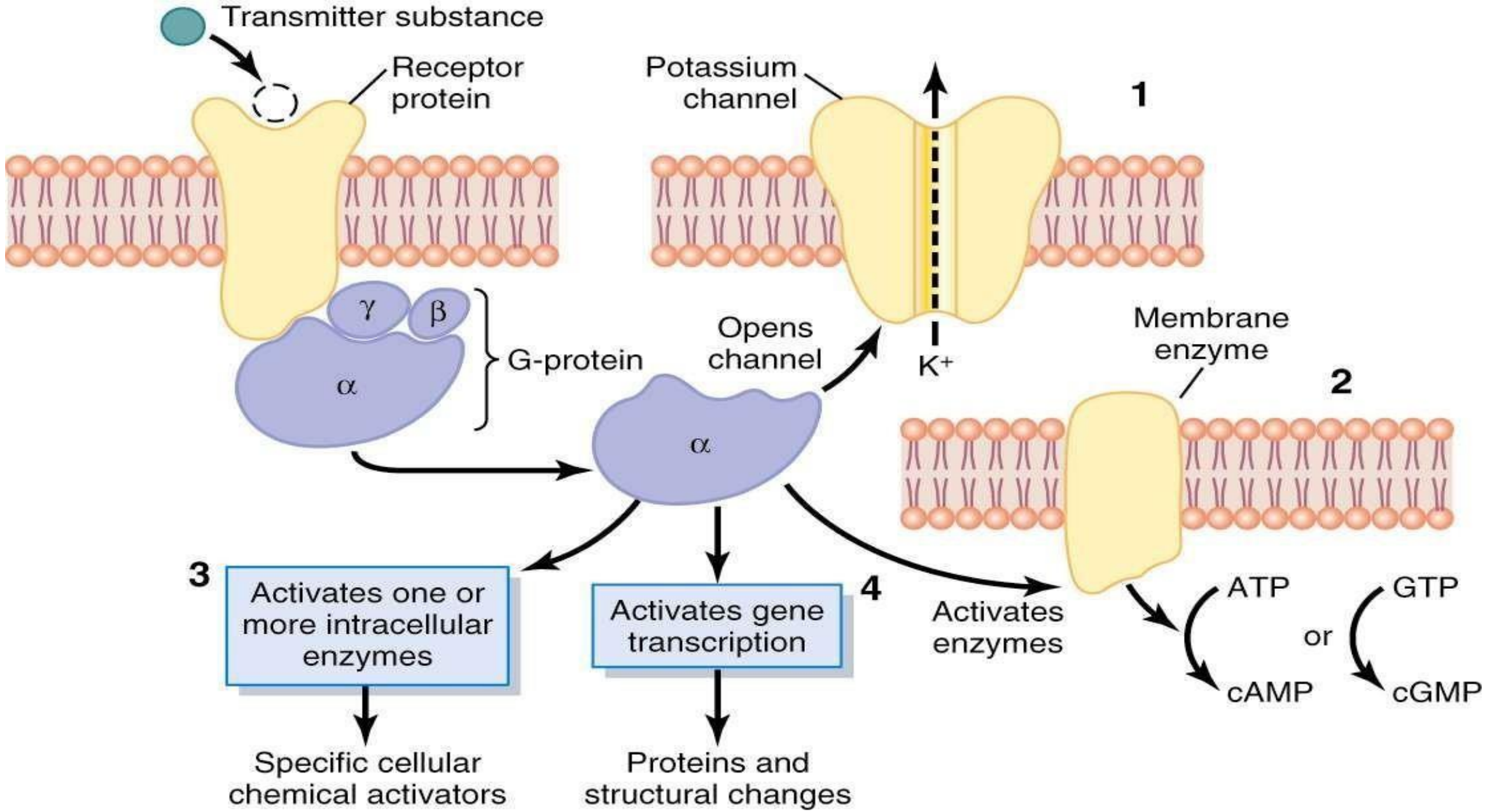
The G protein is composed of beta (β) and gamma (γ) subunits, along with an alpha (α) subunit that is bound to GDP in its inactive state.

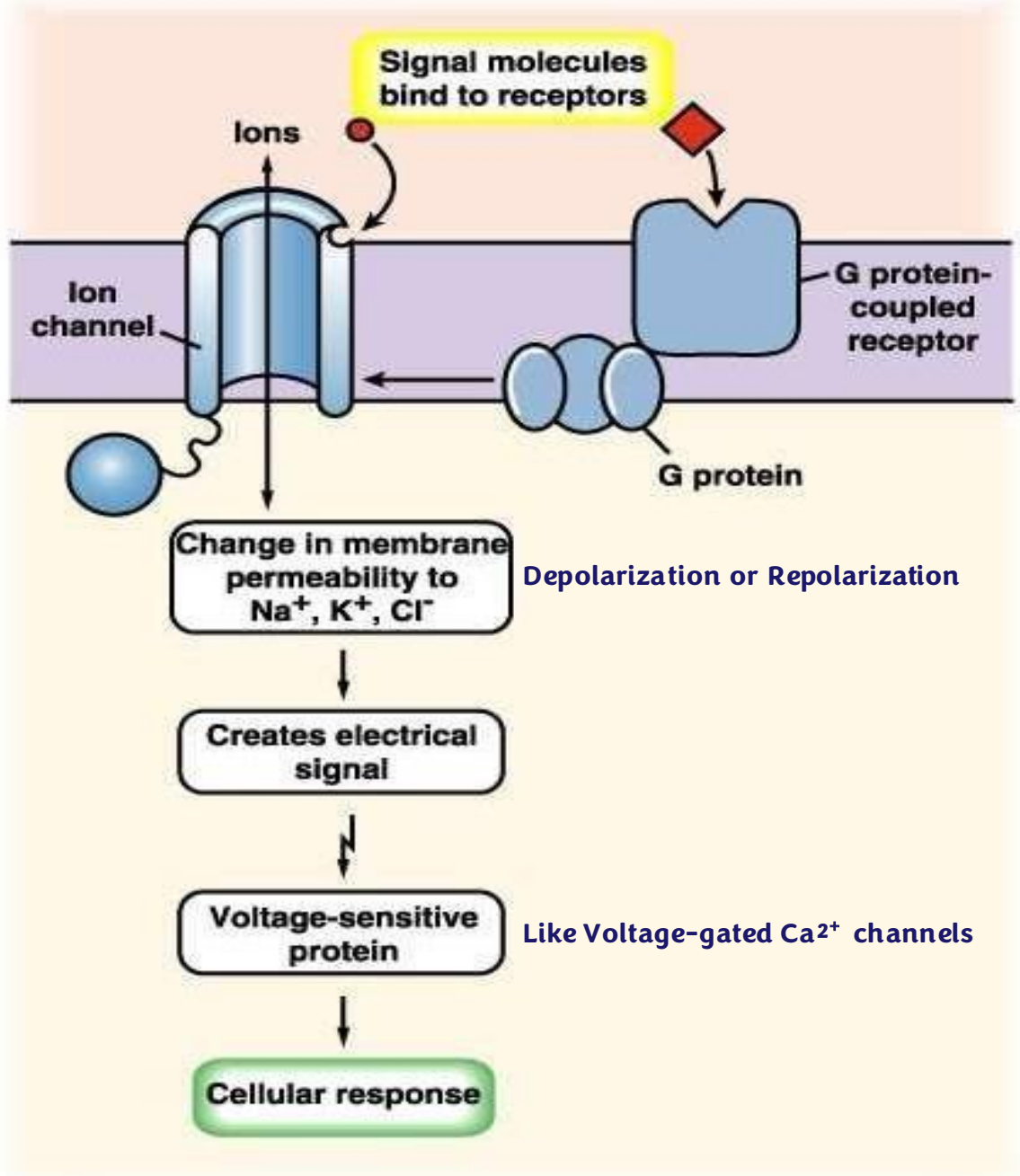
When a hormone or ligand activates the receptor, it catalyzes the exchange of GDP for GTP on the α subunit.

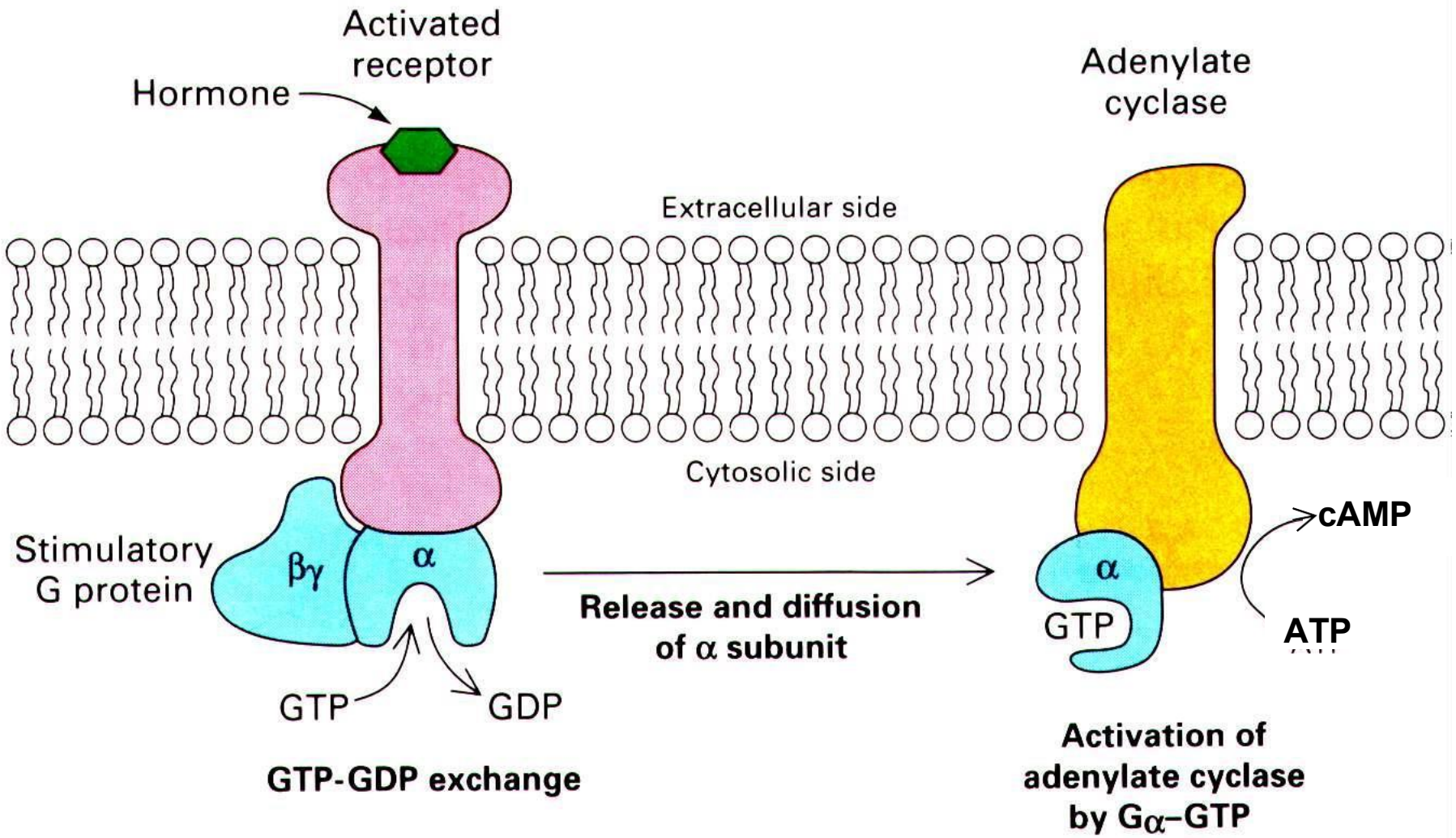
This activates the α subunit, allowing it to dissociate from the βγ complex and go on to activate downstream effectors, such as enzymes or ion channels.



Neurotransmitter or hormone binds to a receptor on the cell surface. Then the G-Protein is Activated. The receptor is linked to a G-protein (made of α, β, and γ subunits). When activated, the α subunit replaces GDP with GTP and breaks away from the βγ subunits. The activated G-protein subunits (α or βγ) stimulate an effector protein or produce intracellular messengers. Or sometimes it can act directly on ion channels and causes them to open or close


Transmitter substance
Receptor protein
Potassium channel
1
γ
β
α
G-protein
Opens channel
K+
Membrane enzyme
2
α
3
Activates one or more intracellular enzymes
Specific cellular chemical activators
Activates gene transcription
4
Proteins and structural changes
Activates enzymes
ATP
or
GTP
cAMP
cGMP


Signal molecules bind to receptors
Ions
Ion channel
G protein-coupled receptor
G protein
Change in membrane permeability to Na^+, K^+, Cl^-
Depolarization or Repolarization
Creates electrical signal
Voltage-sensitive protein
Like Voltage-gated Ca^{2+} channels
Cellular response


Activated
receptor
Hormone
Adenylate
cyclase
Extracellular side
Cytosolic side
Stimulatory
G protein
βγ
α
GTP
GDP
GTP-GDP exchange
Release and diffusion
of α subunit
α
GTP
cAMP
ATP
Activation of
adenylate cyclase
by Gα–GTP

Properties of binding of H and R

- highly specificity
- highly affinity
- Saturation – Vmax & Tmax – (all receptors are bound to hormone)
- reversible binding
- special function model

Receptor Types

- Channel-linked receptors
  - Ionotropic like Ach receptors
- Enzyme-linked receptors
  - Protein kinases → phosphorylation like tyrosine kinase (insulin)
  - Neurotrophins
- G-protein-coupled receptors
  - Metabotropic
- Intracellular receptors
  - Activation by cell-permeant signals ~

Classes of Hormones

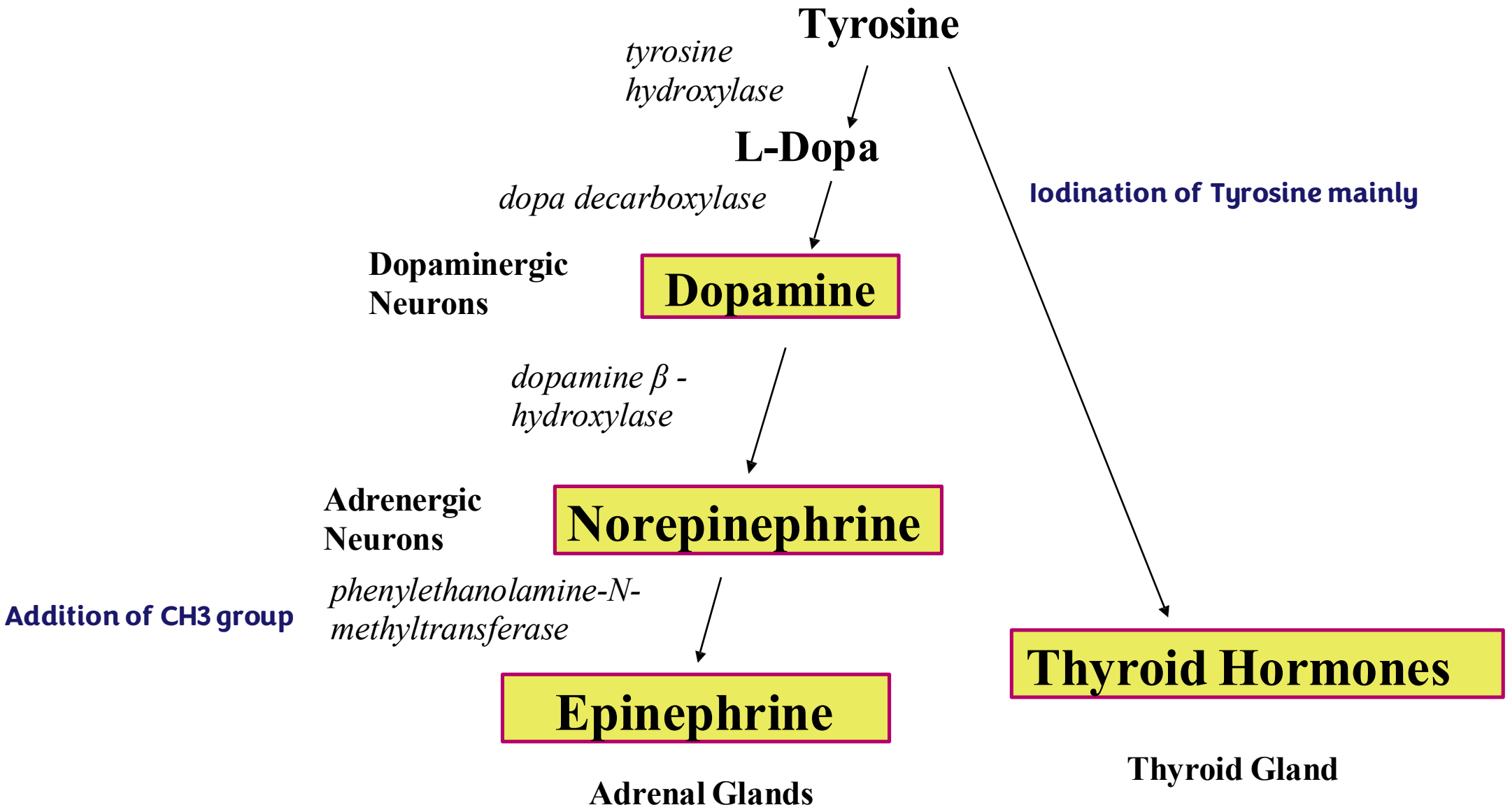
- Peptide & Protein Hormones
- Steroid Hormones
- Amine Hormones (derived from AA)

كَتَبَ رَبُّكُمْ عَلَىٰ نَفْسِهِ الرَّحْمَةَ

Amine Hormones

Gland/Tissue	Hormone
Hypothalamus	Dopamine (derived from tyrosine)
Thyroid	T_3, T_4 (derived from tyrosine)
Adrenal Medulla	Norepinephrine or noradrenaline (NE), epinephrine or adrenaline (EPI)

Synthesis of Amine Hormones



رسالة من الفريق العلمي:

إذا استقرَّ اليقين في القلب، تهاوت أمامه المخاوف كما تتهاوى الظلال عند شروق الشمس.

وما للعبد أن يهاب مخلوقًا ناصيته بيد خالقه، وما له أن يجزع من تدبير البشر، والأقدار كلُّها جاريةٌ بحكم الله.

إنَّ أهل الدنيا يرون الأسباب، وأهل الإيمان يرون مسبِّب الأسباب؛ فإذا اضطربت القلوب سكنت قلوبهم، وإذا فزع الناس اطمأنَّت نفوسهم، لأنهم علموا أنَّ ما شاء الله كان، وما لم يشأ لم يكن.

فوالله لو اجتمع أهل الأرض على ضرِّ عبدٍ أراد الله حفظه ما استطاعوا إليه سبيلًا، ولو اجتمعوا على منع خيرٍ ساقه الله إليه لعجزوا عن ردِّه.

فطوبى لقلبٍ عرف ربَّه، فاستغنى به عن الخلق، وآنسه ذكرُه عن الدنيا، وأورثه التوكُّل عليه عزًّا لا يُغلب، وسكينةً لا تُنزع، ونورًا لا ينطفئ.

- **مُدْرك (محمّد السيّد عبدالوهّاب)**