بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Endocrine Biochemistry | Final 1

Integration of Metabolism

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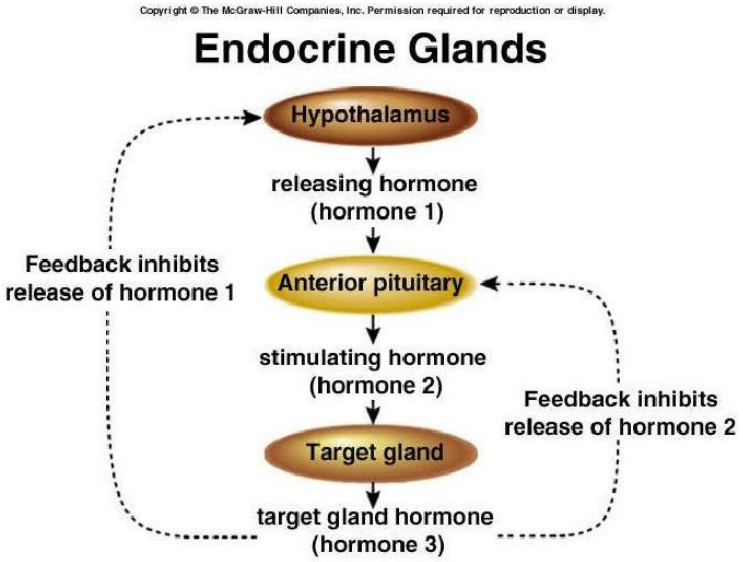
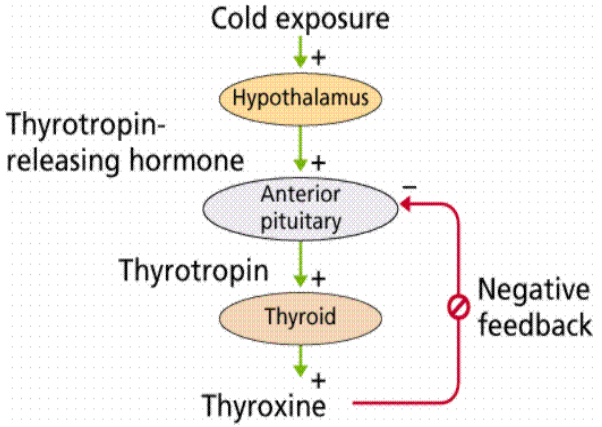
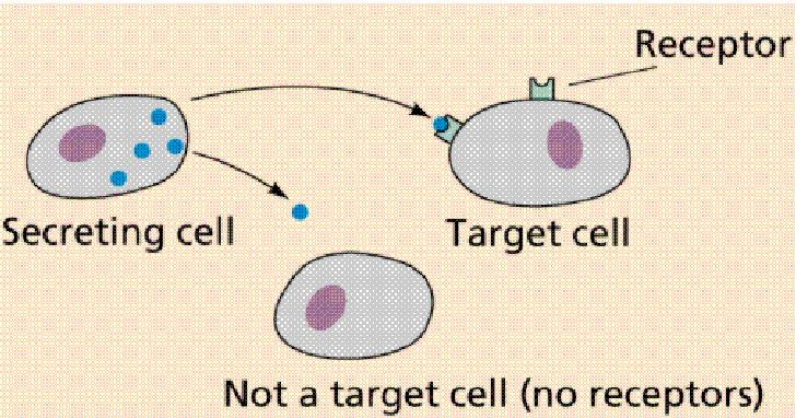
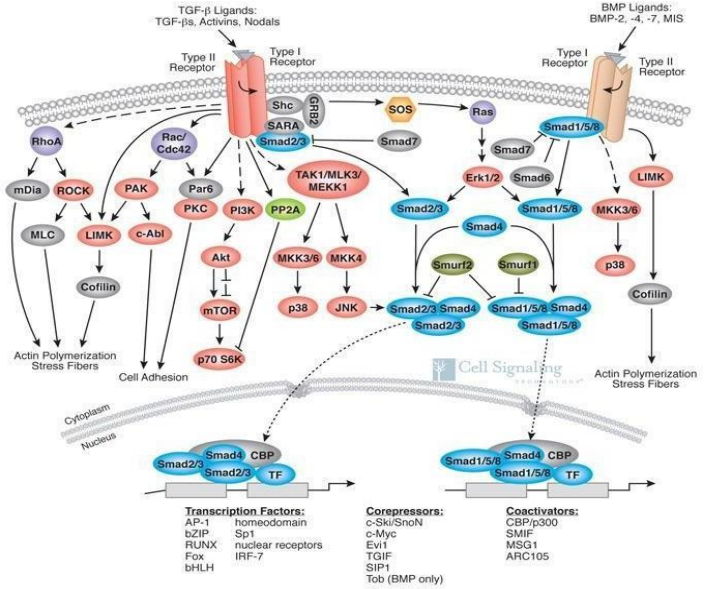
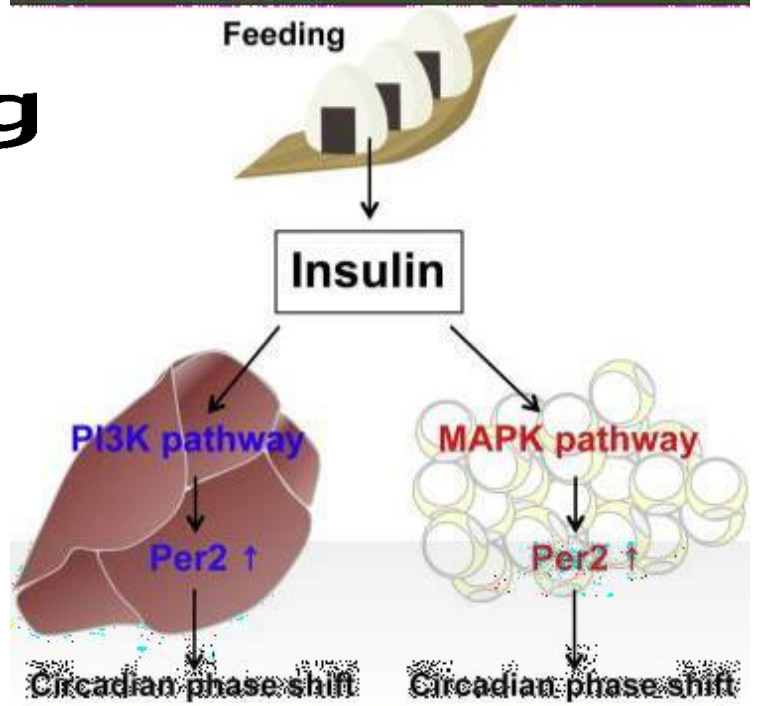
Integration of Metabolism: hormones & Cellular Signaling



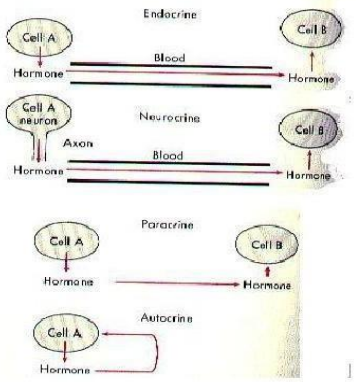








Types of cell-to-cell signaling



Endocrine Hormones: travel via bloodstream to target cells

Neurocrine hormones: released from nerve terminals

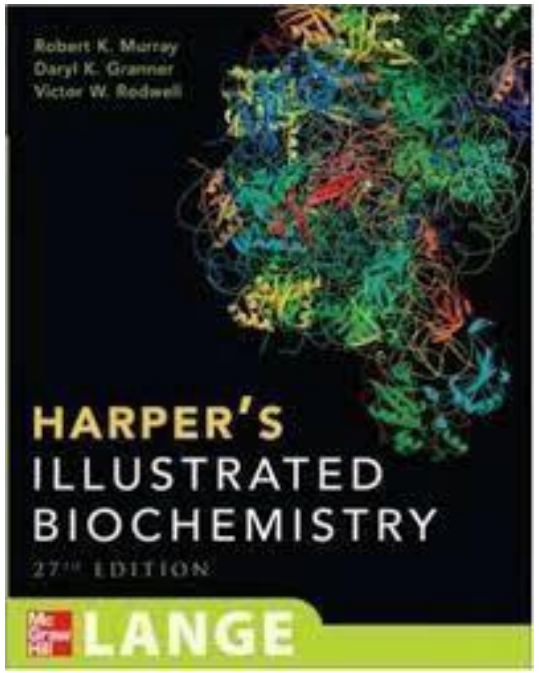
Paracrine hormones: act on adjacent cells

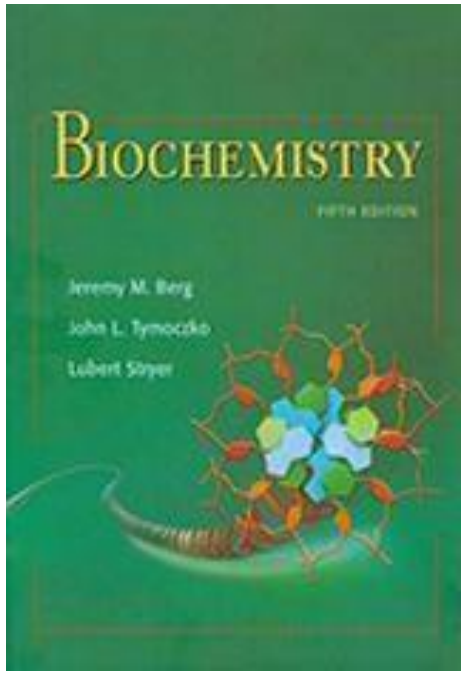
Autocrine hormones: Released and act on the cell that secreted them.

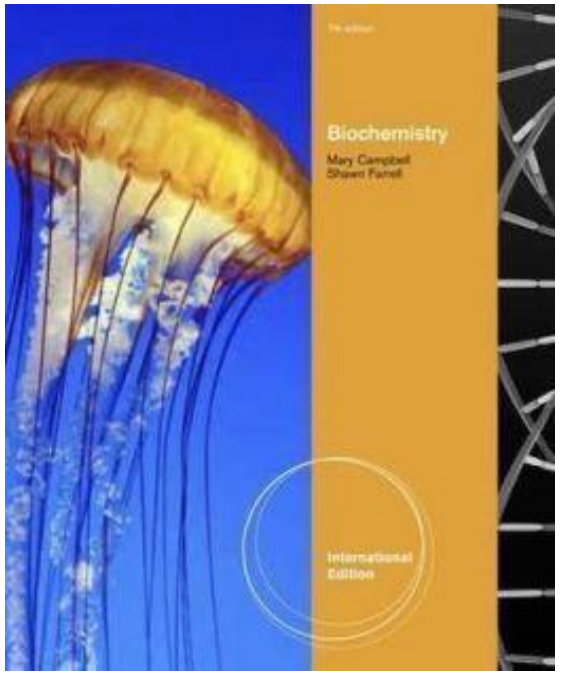
Intracrine Hormones: act within the cell that produces them.

Resources for the lectures

- Harper's Illustrated Biochemistry
- Stryer's Biochemistry
- Campbell's Biochemistry







Outline

1st lecture

- Definition
- Signaling
- Biochemical issues
- Target cell concept
- Receptor domains
- Amplification
- Regulation
- Classification
- Structure, synthesis, and degradation

2nd lecture

- Continued Structure, synthesis, and degradation
- Signal transduction
- 2nd messengers
- GPCR
- G-proteins
- Adenylate cyclase

3rd lecture

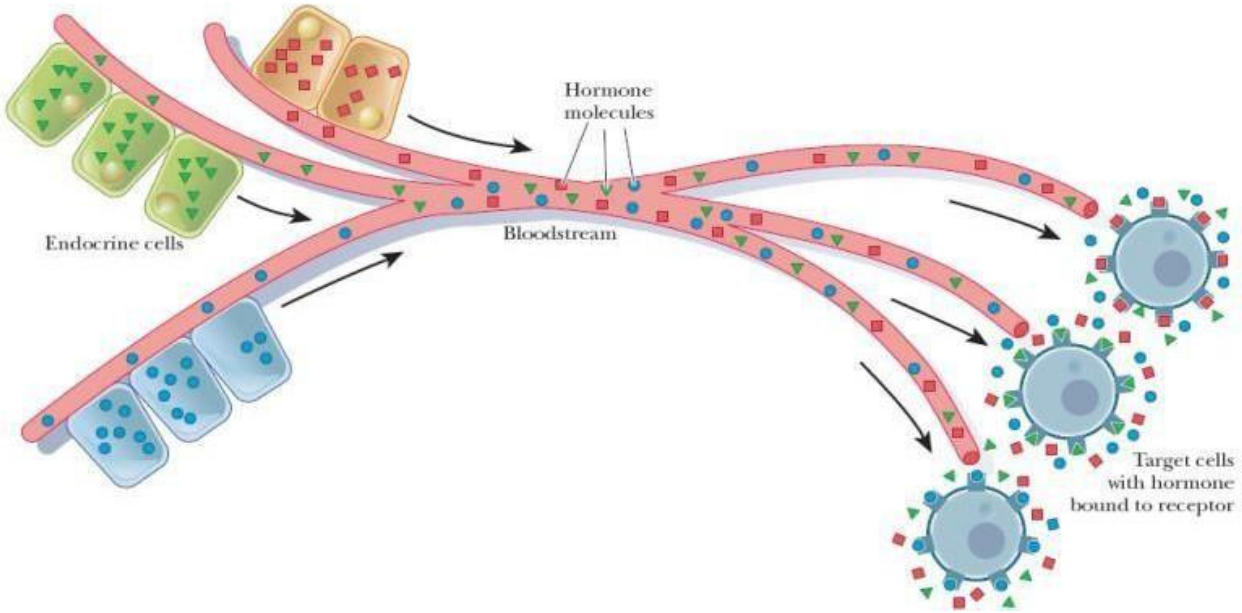
- PI cascade
- Calcium binding proteins
- RTK cascade
- Monomeric G-proteins

4th lecture (online material)

- Steroidogenesis

Hormones: The Remote Controllers

- **What are hormones**? Organic, blood, low amounts, source & target. **(Next Slide).**



- **Classes**:
  - Endocrine hormones
    - Distance; stability; & concentration
  - Paracrine hormones
  - Autocrine hormones

Hormones: The Remote Controllers

❑ ***What are hormones?***

✓ Hormones are transported from the sites of their synthesis to the sites of action by the bloodstream.

✓ They need to be relatively **stable** in the blood and present at an effective **concentration**.

✓ Organic : Carbon Based; Contain Carbon.

➢ In terms of their chemical structure, some typical hormones are :

1) Steroids, such as estrogens, androgens, and mineralocorticoids.
2) Polypeptides, such as insulin and endorphins.
3) Amino acid derivatives, such as epinephrine and norepinephrine.

❑ ***Classes :***

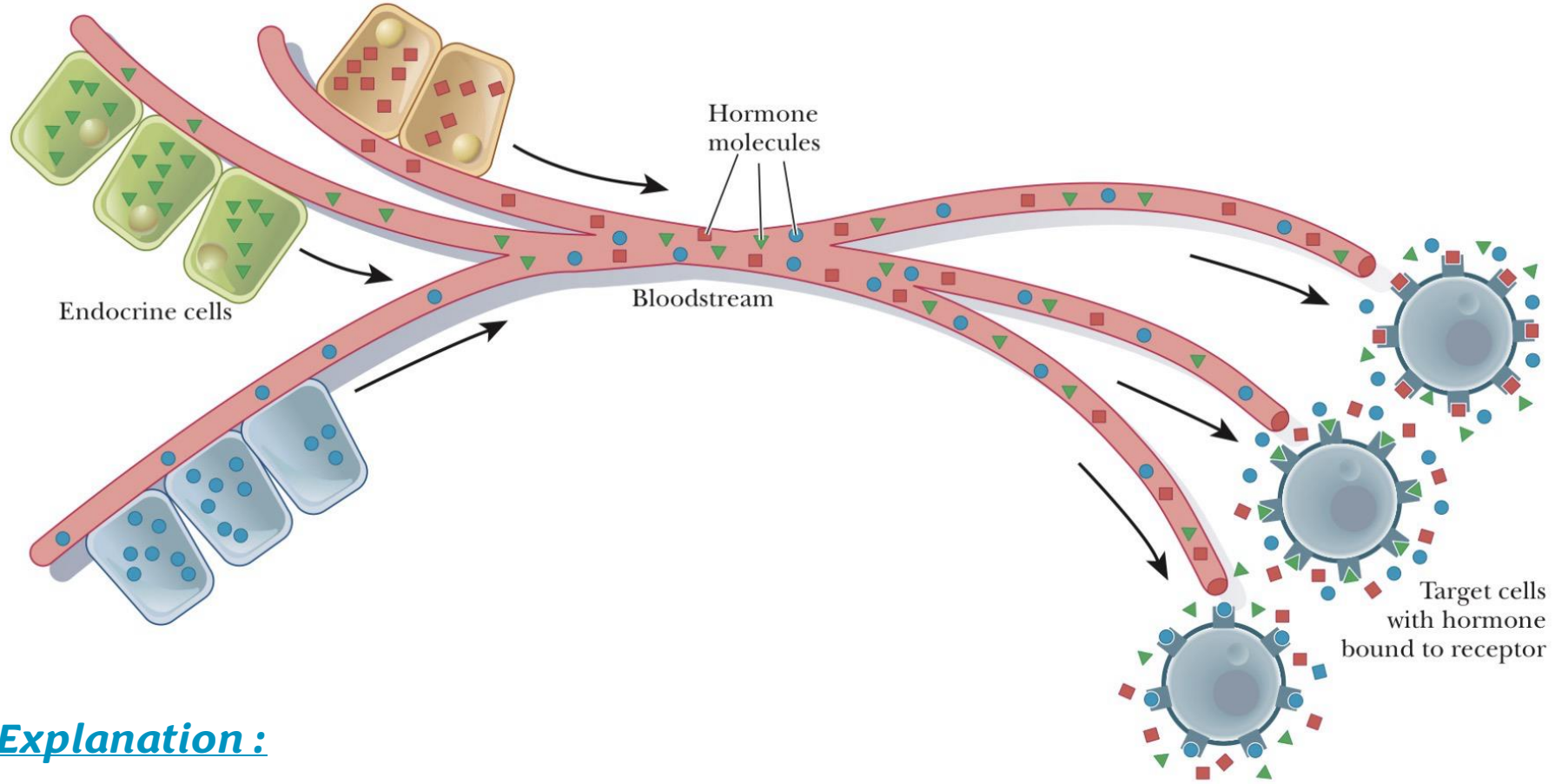
1) Paracrine hormones

- Act on **nearby cells**
- They do **not need to travel through the bloodstream**.
- Example: A cell releases a signaling molecule → it affects a neighboring cell.

2) Autocrine hormones:

- Act on the **same cell that released them**.
- Example: Cell A releases a signaling molecule → that molecule binds to receptors on **Cell A itself**.

Hormones: The Remote Controllers



Picture Explanation :

Blood carries many hormones. Endocrine cells secrete hormones into the bloodstream, which transports them to target cells. Target cells have special receptors that bind to particular hormones, thereby generating their metabolic effect.

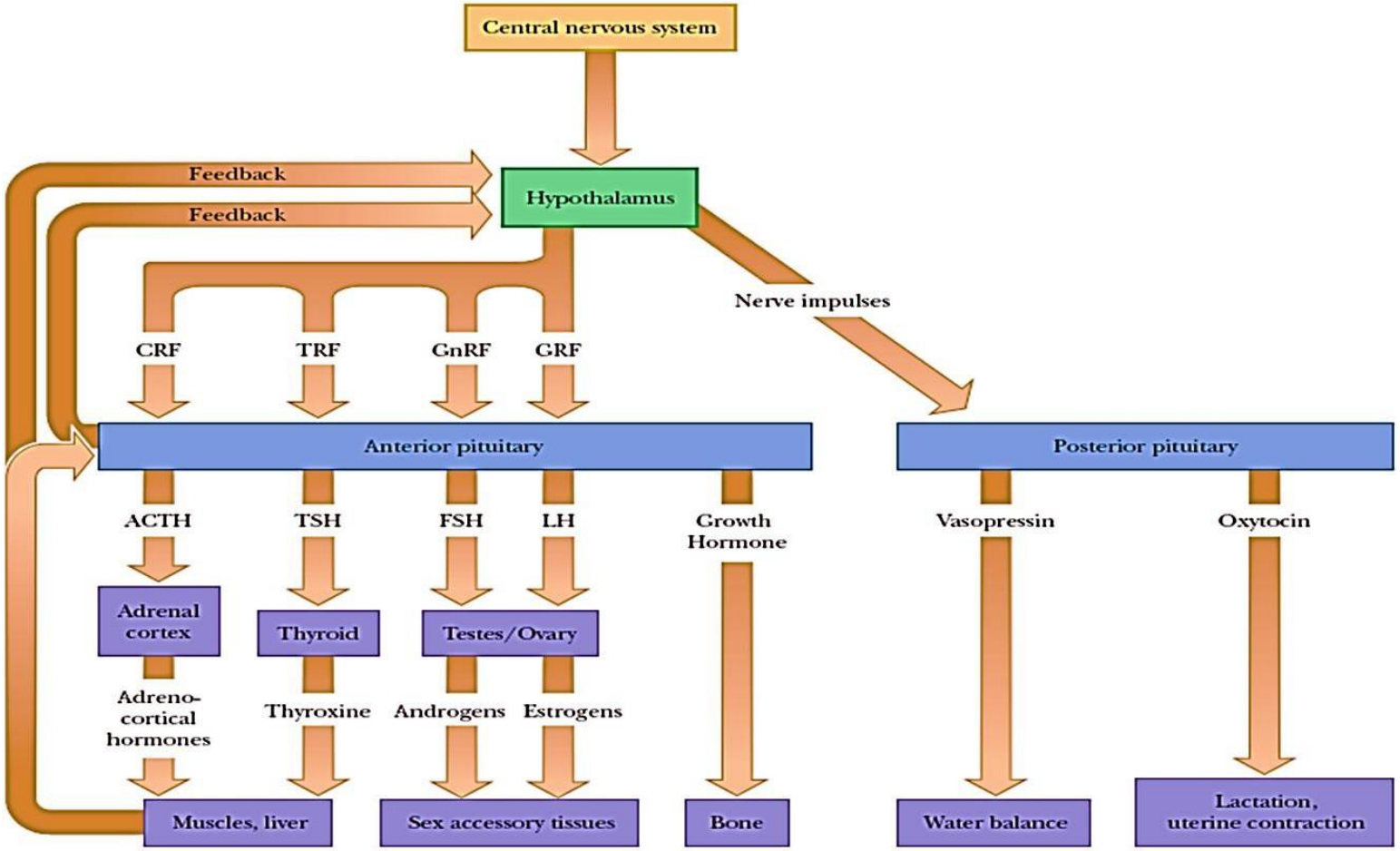
Nervous vs. endocrine

- These two systems are functionally interrelated.

✓ Both regulate human physiology

✓ The endocrine system produces a slower and more prolonged response than the nervous system.

✓ Both systems may act simultaneously on the same target cells and tissues, and some nerve cells secrete hormones (Called Neurohormones).



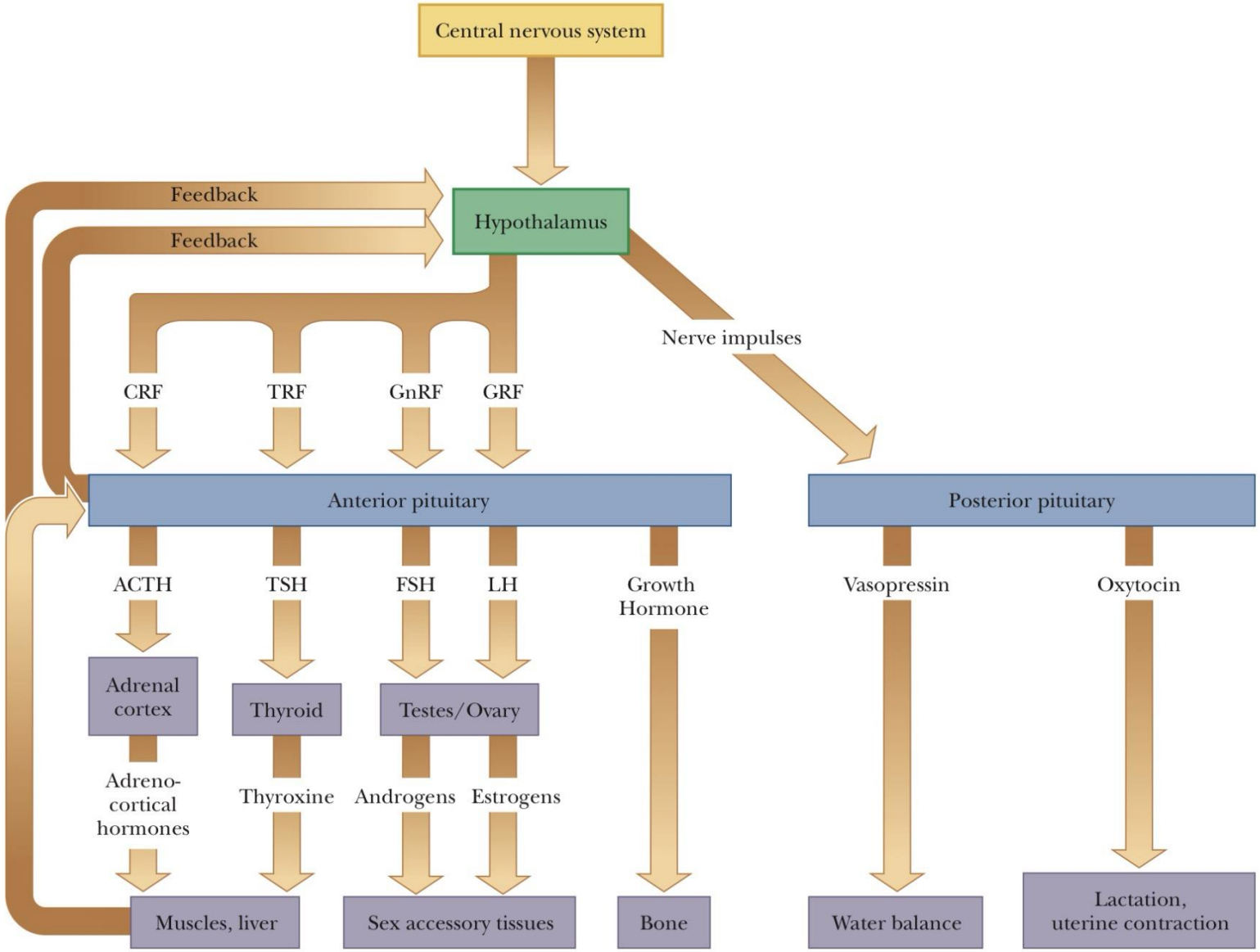
Nervous vs. endocrine

- **The central nervous system** sends a signal to the **hypothalamus**.
- The **hypothalamus** secretes a hormone-releasing factor, which in turn **stimulates release of a trophic hormone by the anterior pituitary**

✓ The action of the hypothalamus on the posterior pituitary is mediated by nerve impulses.

- **Trophic hormones**: act on special **endocrine glands, which release the hormones to be transported to target organs.**

✓ Note that feedback control is exerted at every stage of the process.



The Target Cell Concept

- The definition of a target has been expanded to include any cell in which the hormone (ligand) binds to its receptor, regardless of the action.

- **200 types** of differentiated cells in humans
- Only a few produce hormones! **(<50 known hormones)**
- All of **75 trillion cells** in a human are targets to one or more hormones.

- One hormone → Can affects several cell types.
- One cell type → Can be a target of a several hormones
- One hormone → Can produce several effects (pleiotropy) on different cells.

The Target Cell Concept

- **Several factors determine the response of a target cell to a hormone:**

Factors affect the concentration of the hormone at the target cell
✓ The rate of synthesis and secretion of the hormone
✓ The proximity of the target cell to the hormone source (dilution)
✓ The $\mathbf{K_d}$ of the hormone – receptor complex
✓ The rate of conversion of inactive form to the fully active form
✓ The rate of clearance from the plasma

The Target Cell Concept

- **Several factors determine the response of a target cell to a hormone:**

1. **Rate of synthesis and secretion**
    1. More hormone synthesized and secreted → **higher hormone concentration** → stronger potential response.
2. **Proximity to the hormone source**
    1. The closer the target cell is to the source → less **dilution in the blood** → higher local hormone concentration.
3. **Kd of the hormone-receptor complex (next Slide for more explanation)**
    1. **Kd reflects receptor affinity for the hormone.**
    2. **Low Kd → high affinity** → receptor binds the hormone strongly → response can occur at a lower hormone concentration.
    3. **High Kd → low affinity.**
4. **Conversion of inactive → active hormone**
    1. Some hormones **must be converted** into their **active form** before they can produce their full effect.
    2. Example: **T4 → T3.**
5. **Rate of clearance from plasma**
    1. **High clearance** → hormone is removed quickly → lower concentration and shorter duration.
    2. **Low clearance** → hormone stays longer → prolonged effect.

The Target Cell Concept

- **Several factors determine the response of a target cell to a hormone:**

Factors affecting the target cell response
✓ The number, relative activity, and state of occupancy of receptors
✓ The metabolism (activation / inactivation) of the hormone in the target cell
✓ The presence of factors within target cell necessary for the response
✓ Up- or down-regulation of the receptors upon interaction with ligand ✓ Post-receptor desensitization of the cell

The Target Cell Concept

- **Several factors determine the response of a target cell to a hormone:**

1. Number, activity, and occupancy of receptors

The response depends on:

- **Number of receptors:** More receptors → more hormone can bind → **generally stronger response.**
- **Relative activity (Nature of the receptor itself) :** How effectively the receptors activate their signaling pathway.
- **Occupancy:** How many receptors are currently occupied by hormone.

2. Hormone metabolism inside the target cell

- The target cell can **activate or inactivate** the hormone.
  - **Activation** → **increases** the hormone's effect.
  - **Inactivation** → **decreases** the hormone's effect.

Example: **T4** → **T3**
T4 is converted to the more active thyroid hormone T3 in peripheral tissues. (Increases the response).

The Target Cell Concept

- **Several factors determine the response of a target cell to a hormone:**

3. Necessary intracellular factors

- Even if the hormone binds perfectly to its receptor, the cell needs the necessary **intracellular machinery** to produce the response. (If it is defected due to genetic factor, it will decrease the effect of the cellular response to the hormone).

➢ For example:
- **Hormone → Receptor → Signaling pathway → Cellular response**
- If an essential component of this pathway is missing → **little or no response**.

4. Up- or down-regulation of receptors

- When a hormone repeatedly interacts with its receptor, the cell can change the **number/sensitivity of receptors**.

- **Up-regulation** → More receptors → **Increased sensitivity** to the hormone.

- **Down-regulation** → Fewer receptors → **Decreased sensitivity** to the hormone.

The Target Cell Concept

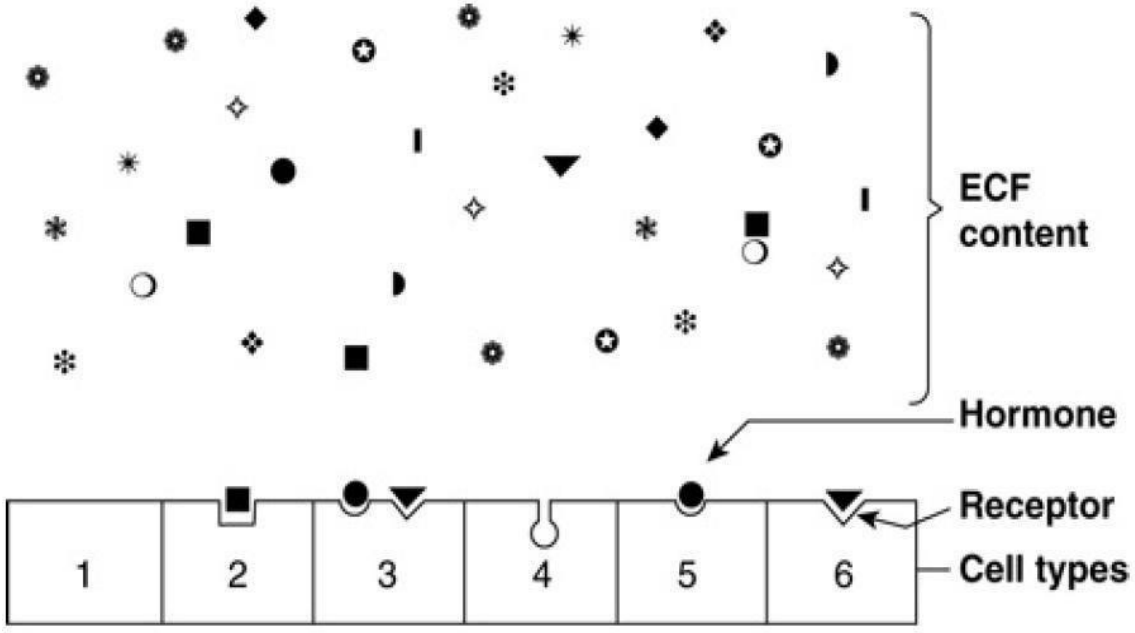
- **Several factors determine the response of a target cell to a hormone:**

5. Post-receptor desensitization

- This is slightly different from the up and down regulation (normal sensitisation & desensitisation).
- The hormone **still binds to its receptor**, but the cell becomes less responsive **after the receptor**.
- So: **Hormone → Receptor → ↓ signaling response**
- The receptor may be present, **but the intracellular signaling machinery becomes less responsive**.

Receptors Discriminate Precisely

- **Major challenge**: **(Explanation is in the next Slide).**
  - Atto- to nano-molar range (10^{-15} to 10^{-9} mol/L) vs. Structurally similar molecules (sterols, amino acids, peptides, and proteins): micro- to milli-molar (10^{-6} to 10^{-3} mol/L) range



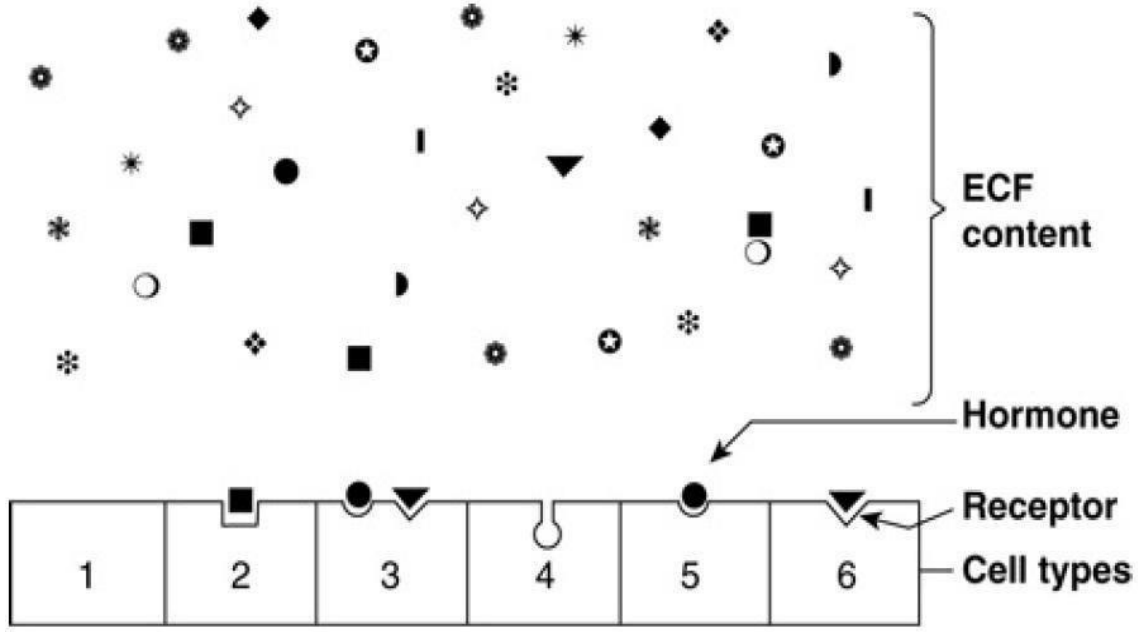
Receptors Discriminate Precisely

1. Hormones are present in very low concentrations

Hormones usually circulate at approximately: **10^{-15} to 10^{-9} mol/L → femtomolar to nanomolar range**
In contrast, many other molecules in the extracellular fluid are present at much higher concentrations: **10^{-6} to 10^{-3} mol/L → micromolar to millimolar range**
So hormones are present at concentrations **millions to billions of times lower** than many other molecules.

2. How can a cell recognize the correct hormone?

Imagine a target cell surrounded by **millions of different molecules**.
The cell needs to distinguish:
"This specific molecule is my hormone."
It does this using **specific receptors**.
A receptor is like a **lock**, and the correct hormone is the **key**.
Hormone → specific receptor → biological effect
Only cells that have the appropriate receptor are **target cells** for that hormone.



Receptors Discriminate Precisely

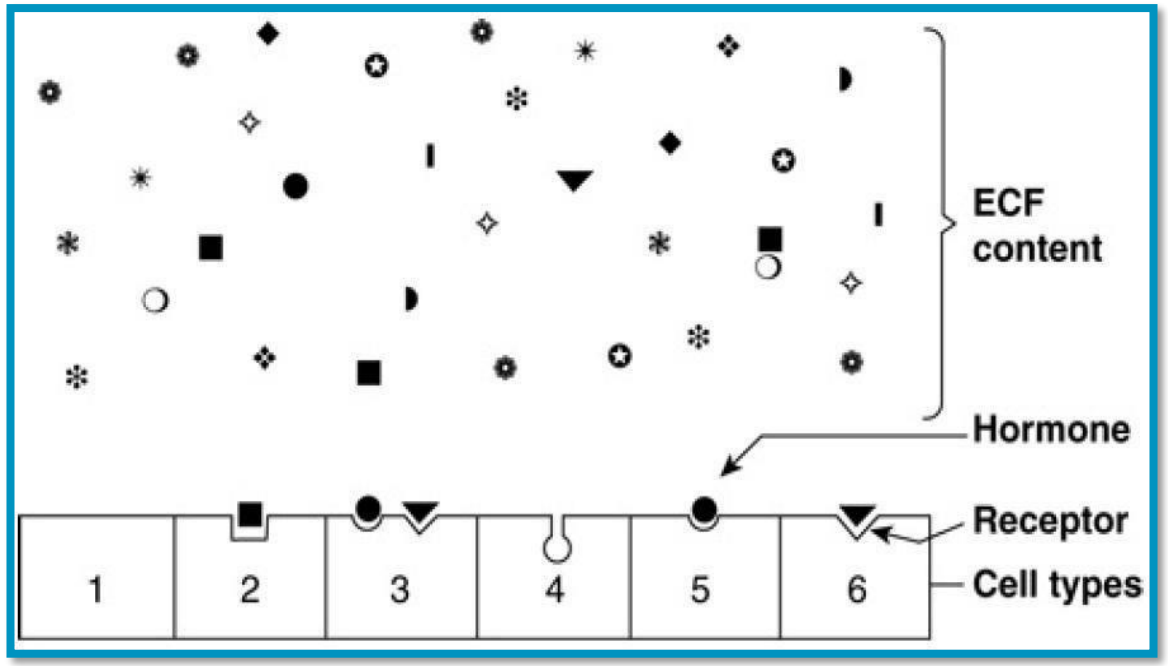
3. What happens after the hormone binds?

The hormone binds to its specific receptor and **initiates a biological response**.
When the hormone **dissociates (unbinds)** from the receptor, the response generally stops.
So:
Hormone binds → response ON
Hormone unbinds → response OFF
This is important because the body needs a way to **terminate the hormone's effect**.

4. What defines a target cell?

A **target cell** is a cell that has the ability to **specifically bind a particular hormone to its cognate (matching) receptor**.
Therefore:
No receptor → no specific response → not a target cell.

Receptors Discriminate Precisely

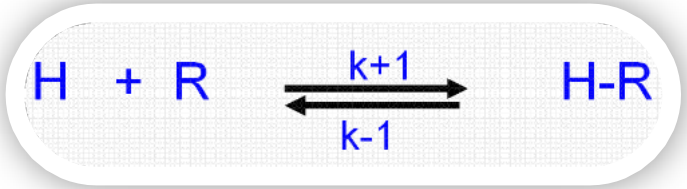


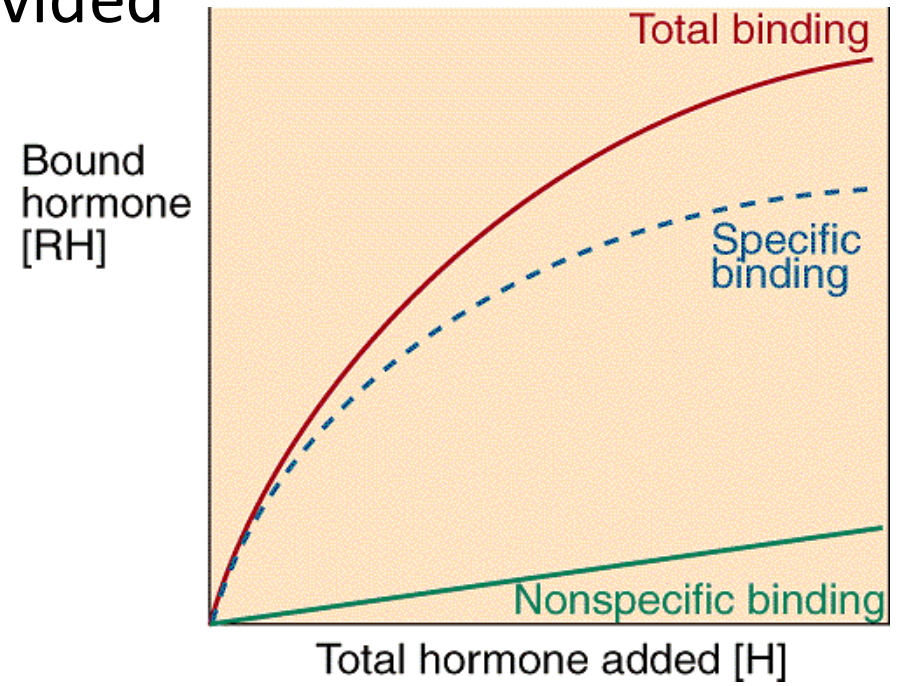
Specificity and selectivity of hormone receptors.

Many different molecules circulate in the extracellular fluid (ECF), but only a few are recognized by hormone receptors. Receptors must select these molecules from among high concentrations of the other molecules. This simplified drawing shows that a cell may have no hormone receptors (Cell type 1), have one receptor (Cell types2+5+6), have receptors for several hormones (Cell type 3), or have a receptor but no hormone in the vicinity (Cell type 4).

Accordingly; Hormone-Receptor interactions

- Should be **specific**: displaceable by agonist or antagonist
- Should be **saturable**
- Should occur within the **concentration range** provided





- Dissociation constant K_d
  - $K_d = \{[H] \times [R]\} / [H\text{-}R]$
- 20 X dissociation constant **(Kd)** is enough to saturate the receptor
- **K_d** values for many hormone range from 10^{-9} to 10^{-11} M

Accordingly; Hormone-Receptor interactions

Characteristics of hormone–receptor binding

The paragraph gives **3 important properties**:

① **Specific:**
The receptor should recognize the correct hormone.
- It should also be possible to interfere with this binding using an **agonist or antagonist**.
- **Agonist** → binds and activates the receptor.
- **Antagonist** → binds but blocks the receptor's activation.

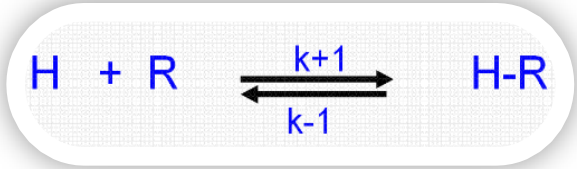
② **Saturable:**
There is a **limited number of receptors**.
Therefore, once all receptors are occupied:
Adding more hormone cannot keep increasing receptor occupancy indefinitely.
Think of a parking lot:
- 100 parking spaces = 100 receptors
- Once all 100 are occupied → the parking lot is **saturated**.

③ **Occurs within the physiological concentration range:**
The hormone must bind to its receptor at concentrations that actually occur in the body.

Explanation of the Kd (Disassociation Concept)

Kd is a measure of how tightly a hormone holds onto its receptor.

The reaction is:



- **H** = hormone
- **R** = receptor
- **HR** = hormone–receptor complex

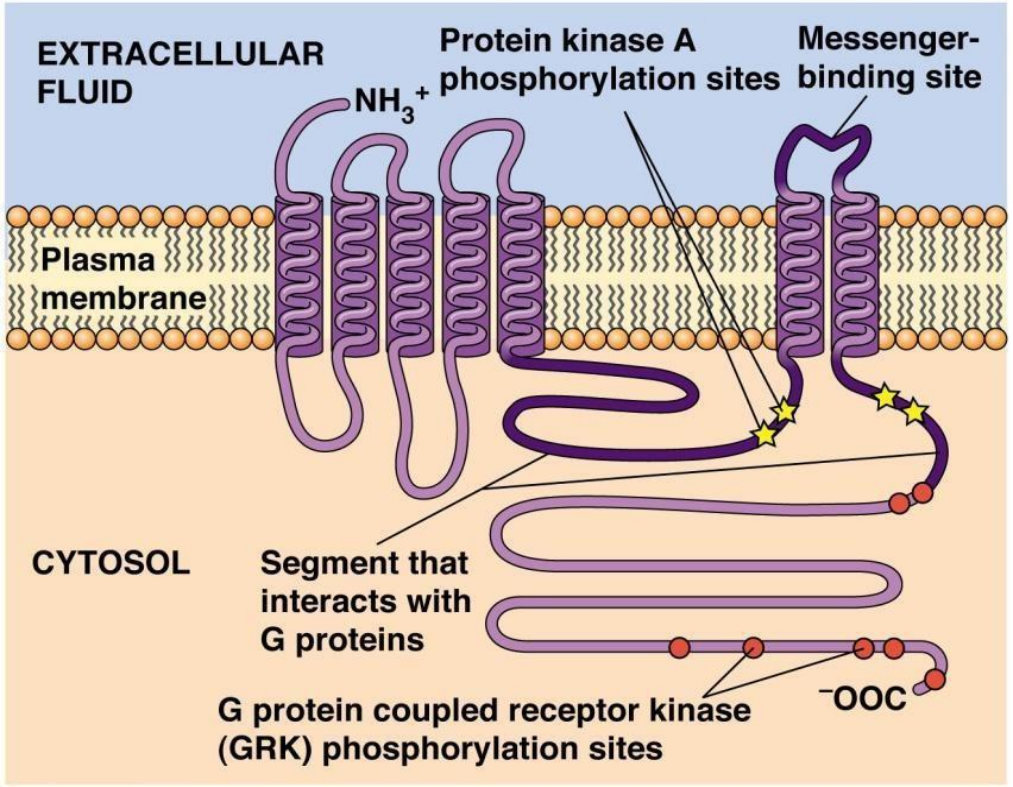
❑ ***<u>What does Kd actually tell you?</u>***

✓ **Kd is the hormone concentration at which approximately 50% of the receptors are occupied.**

For example:

Suppose you have **100 receptors**.
If: Kd = 10^{-9} then when the hormone concentration is approximately 10^{-9} M about **50 receptors are occupied** and 50 are free.

Receptor domains



- All receptors have at least two functional domains:
  - **Recognition domain**
  - **Coupling or signal transduction domain**
- Coupling occurs in two general ways:
  - Changing the activity of an enzyme (Polypeptide & catecholamines, plasma membrane)
  - Direct (steroids, retinoids, and thyroid hormones, intracellular)
- Steroid, thyroid, and retinoid hormone receptors:
  - Hormone binding site ; DNA binding site; co-regulator proteins binding site, cellular trafficking proteins binding site
- Receptor–effector coupling provides the first step in amplification

Receptor domains (Explination)

❑ **Hormone receptors have at least two functional domains :**

- A **recognition** domain binds the hormone ligand.
- Region **generates a signal** that couples hormone recognition to some intracellular function.

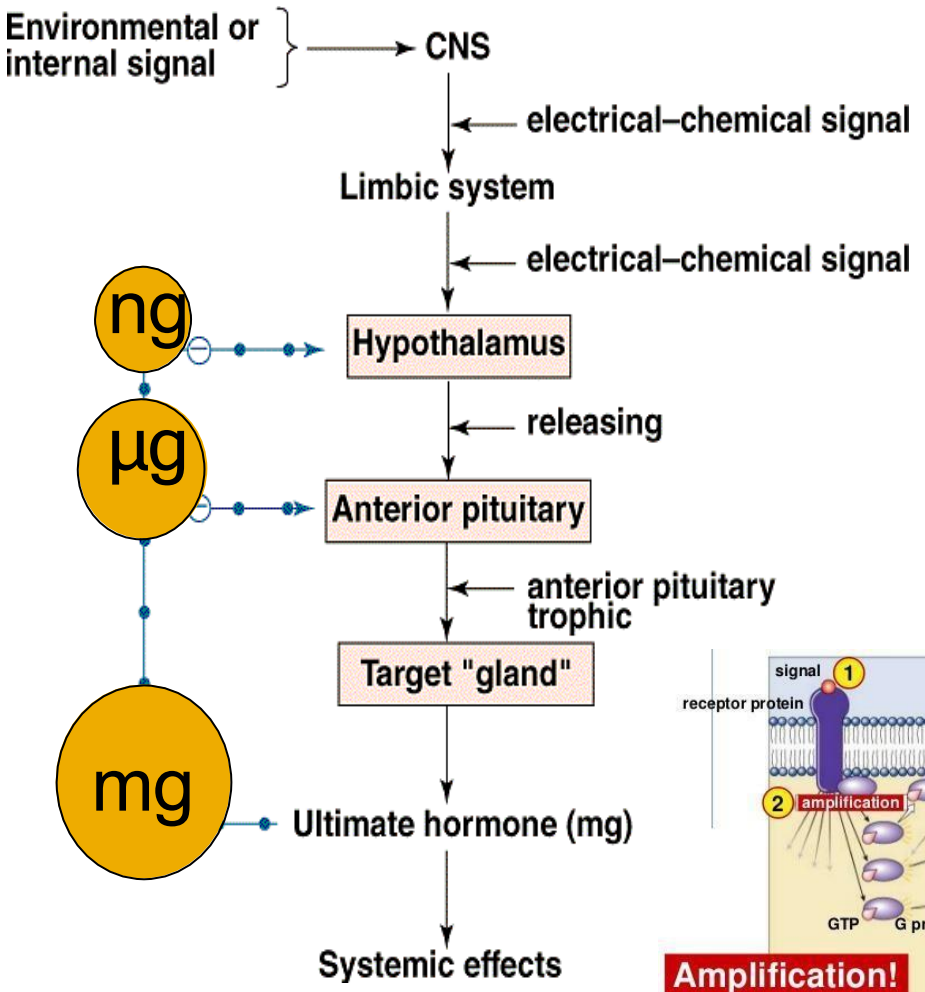
❑ **This coupling, or signal transduction, occurs in two general ways :**

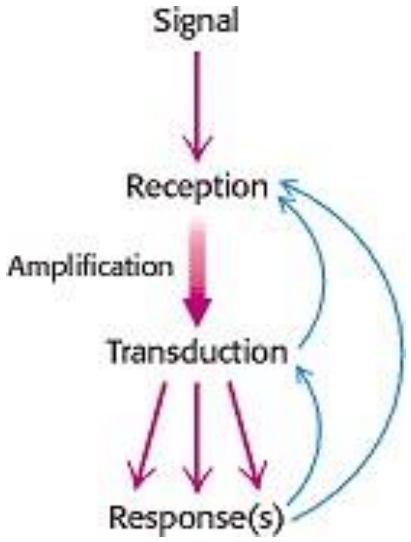
- **Polypeptide** and **protein hormones** and the **catecholamines** bind to receptors located in the plasma membrane and thereby generate a signal that regulates various intracellular functions, often by changing the activity of an enzyme.

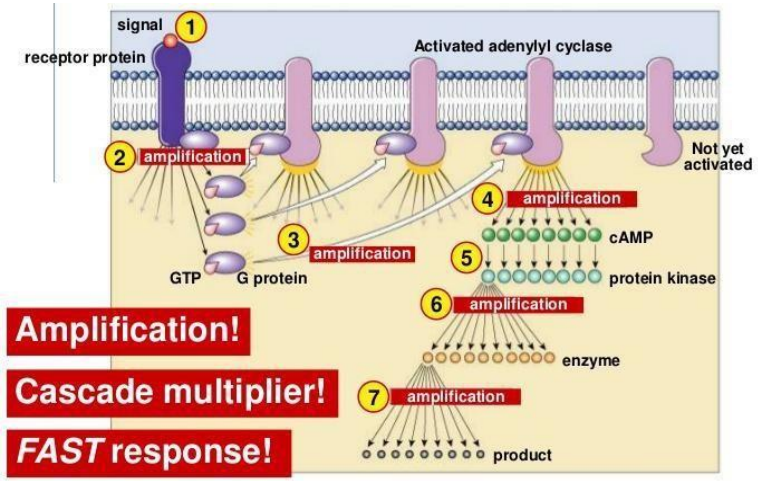
- **Lipophilic steroid, retinoid, and thyroid hormones** interact with intracellular receptors, and it is this ligand-receptor complex within the nucleus that directly provides the signal, generally to specific genes whose rate of transcription is thereby affected.

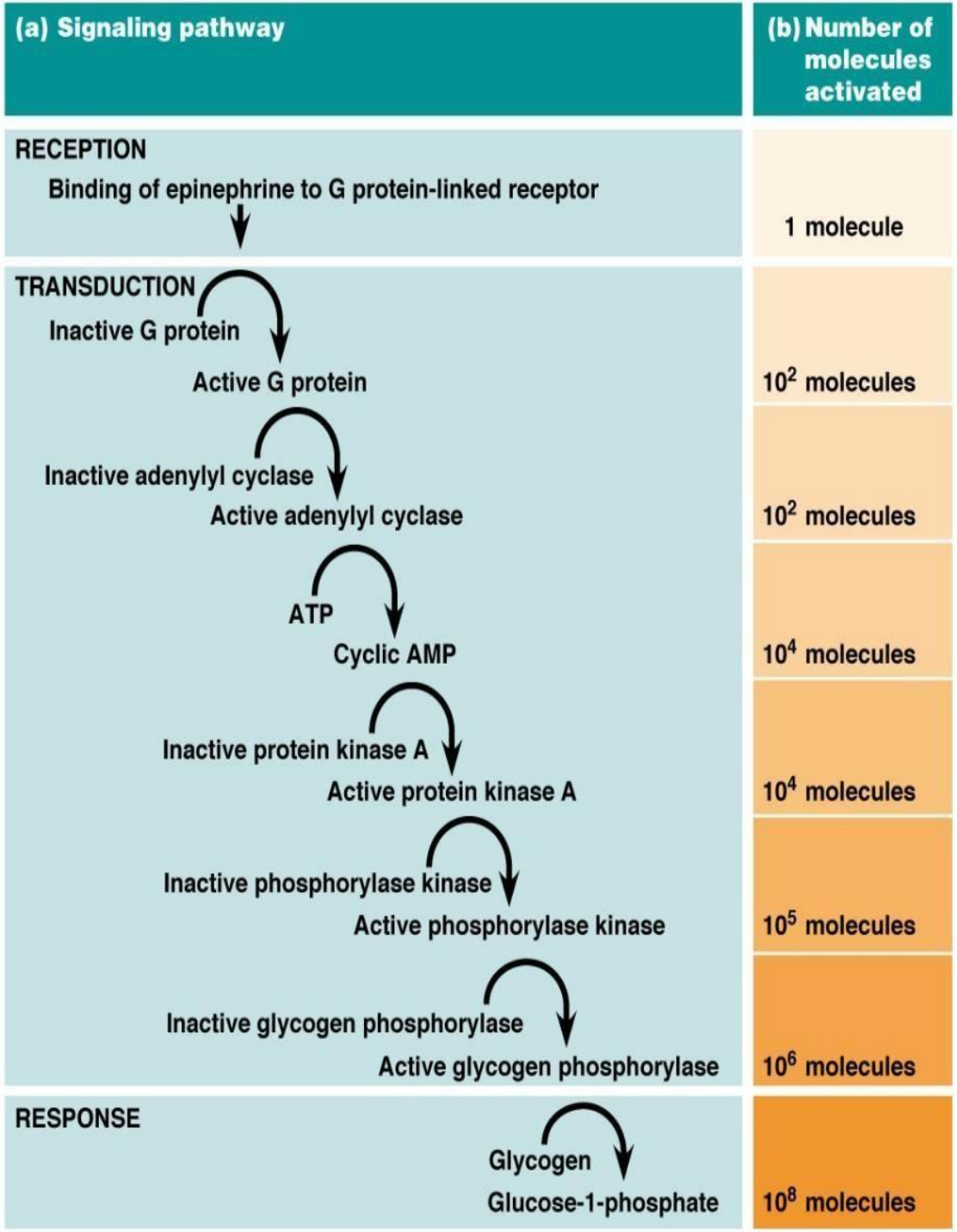
- The domains responsible for hormone recognition and signal generation have been identified in the protein/polypeptide and catecholamine hormone receptors. Like many other DNA-binding transcription factors, the steroid, thyroid, and retinoid hormone receptors have several functional domains: one site binds the hormone; another binds to specific DNA regions; a third is involved in the interaction with various coregulator proteins that result in the activation (or repression) of gene transcription; and a fourth region may specify binding to one or more other proteins that influence the intracellular trafficking of the receptor.

Signal Amplification









Signal Amplification (Explanation)

- **A very small signal can produce a very large response**.
- Imagine that we have only one molecule of a hormone, such as epinephrine.
- That one molecule binds to its receptor on the cell membrane, but it doesn't produce the response directly. Instead, **it starts a cascade of reactions inside the cell.** And this is where the ***amplification*** happens.
- ***The first step is reception :*** Epinephrine binds to a G protein-coupled receptor, or GPCR, on the cell membrane. Once the receptor is activated, it activates G proteins.
- Notice: **one initial signal can activate many G protein molecules.** So we have our **first amplification**.
- These activated G proteins **then activate an enzyme called adenylyl cyclase. Adenylyl cyclase converts ATP into cyclic AMP, or cAMP.** And cAMP is very important because **we can produce a large number of cAMP molecules from the activity of these enzymes** (we go from approximately 10^2 molecules to 10^4 molecules).
- Then cAMP activates protein kinase A (PKA). PKA is a kinase, **meaning that it phosphorylates and activates other proteins.** PKA activates **phosphorylase kinase**, which then activates glycogen phosphorylase (As an Example).

Signal Amplification (Explanation)

- **<u>And now we reach the final response :</u>**Glycogen phosphorylase **breaks down glycogen, producing glucose-1-phosphate.**

- So look at what happened:

- ***1 epinephrine molecule →10^2 G proteins →10^2 adenylyl cyclase molecules →10^4 cAMP molecules →10^4 PKA molecules →10^5 phosphorylase kinase molecules →10^6 glycogen phosphorylase molecules →approximately 10^8 glucose-1-phosphate molecules***

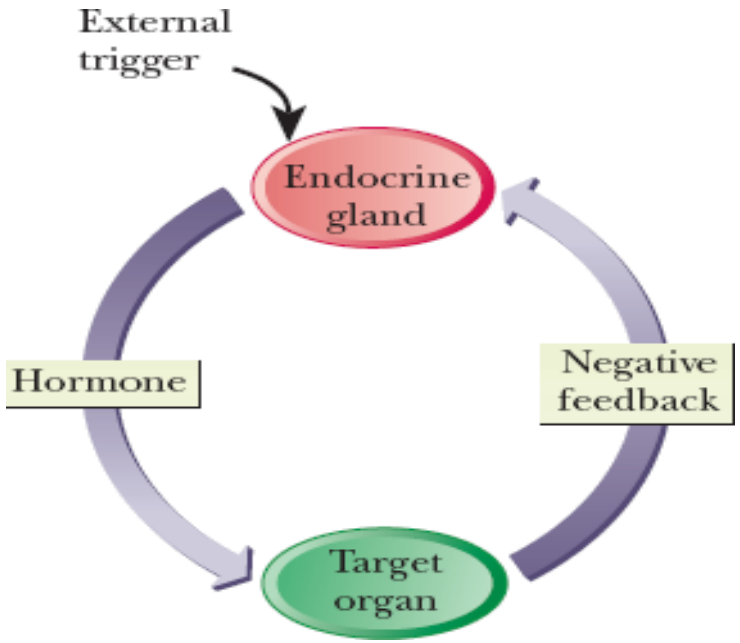
- ***So we started with one molecule, and eventually we produced around 100 million molecules of product*** → That is what we mean by signal amplification.

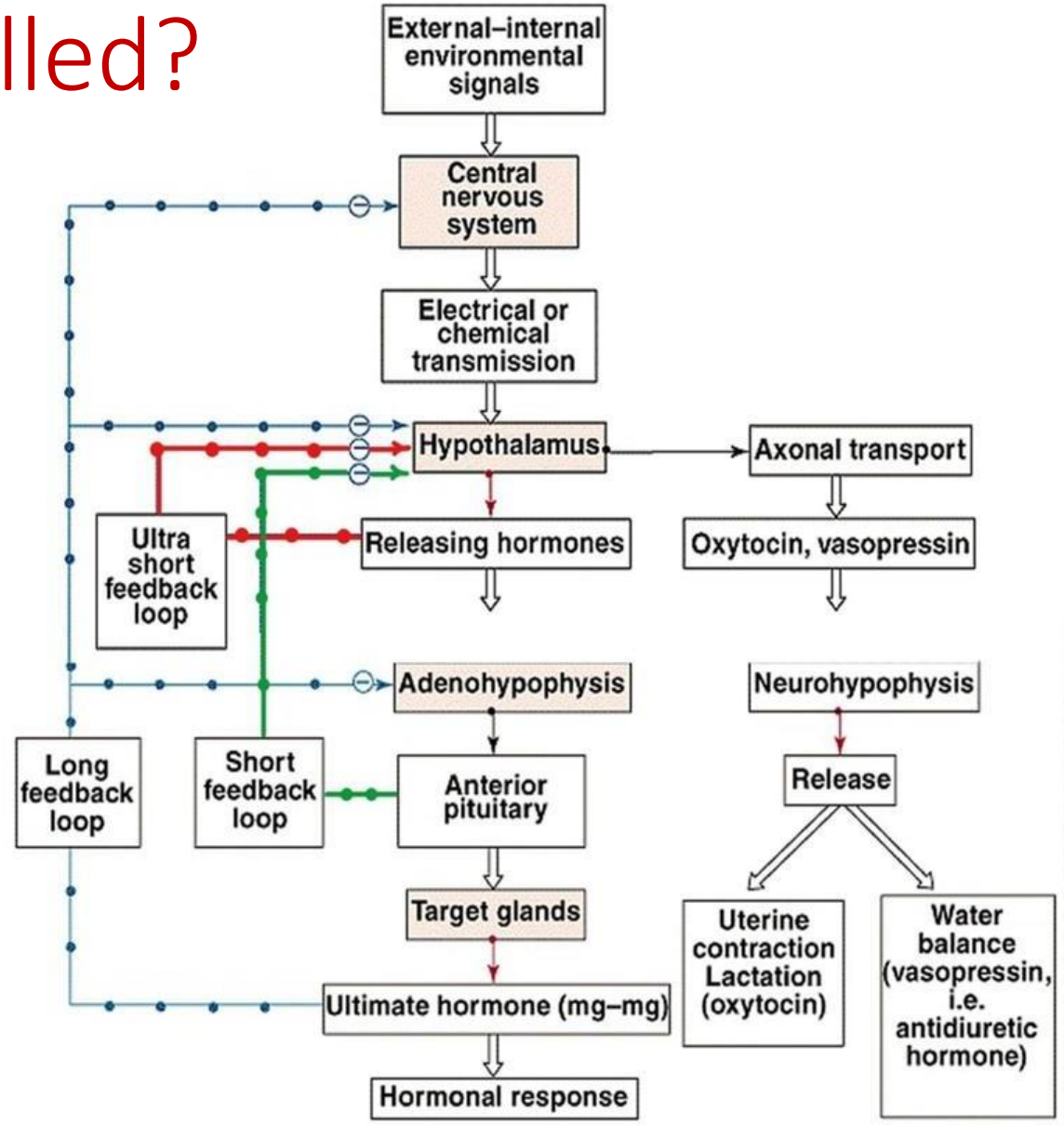
❑ **<u>Why does the body use amplification?</u>**

✓ The advantage is that the body can produce a very rapid and powerful response **without needing a large amount of the original signal.**

How the release is controlled?

- **Feedback inhibition**
  - **Ultrashort loop**
  - **Short loop**
  - **Long loop**





How the release is controlled?

***Feedback inhibition* :**

- The basic idea is that when a hormone is released and produces its effect, the hormone or its downstream products can **feed back and reduce further hormone release**.

❑ **Why do we need this?**

Because the endocrine system should not keep producing hormones continuously. We want the response to be **controlled and balanced**.

Now we have three types of feedback loops
The difference between them is basically **where the feedback goes back to** :

1. Ultrashort feedback loop
This is the **shortest loop**.
The hypothalamus releases a **releasing hormone**, and that same releasing hormone can provide feedback directly to the **hypothalamus itself** and reduce further release.
So: **Hypothalamus → Releasing hormone → feedback to hypothalamus**
The important point is:
The hypothalamus regulates itself.
That's why we call it **ultrashort**—the feedback doesn't need to travel far.

How the release is controlled?

2. Short feedback loop

- The **hypothalamus** releases a releasing hormone → this stimulates the **anterior pituitary** → the anterior pituitary releases a **tropic hormone**.
- That pituitary hormone can then feed back and inhibit the **hypothalamus**.
- So: **Hypothalamus → Releasing hormone → Anterior pituitary → Tropic hormone → feeds back to the hypothalamus.**

- This is called a **short feedback loop** because the feedback comes from the **pituitary**, which is **relatively close to the hypothalamus in the endocrine pathway.**

3. Long feedback loop

- The hypothalamus releases a releasing hormone → That stimulates the anterior pituitary → The anterior pituitary releases a **tropic hormone** → The tropic hormone stimulates the **target endocrine gland** → The target gland then produces the **ultimate hormone** → ultimate hormone feeds back and inhibits the **hypothalamus and/or anterior pituitary**.

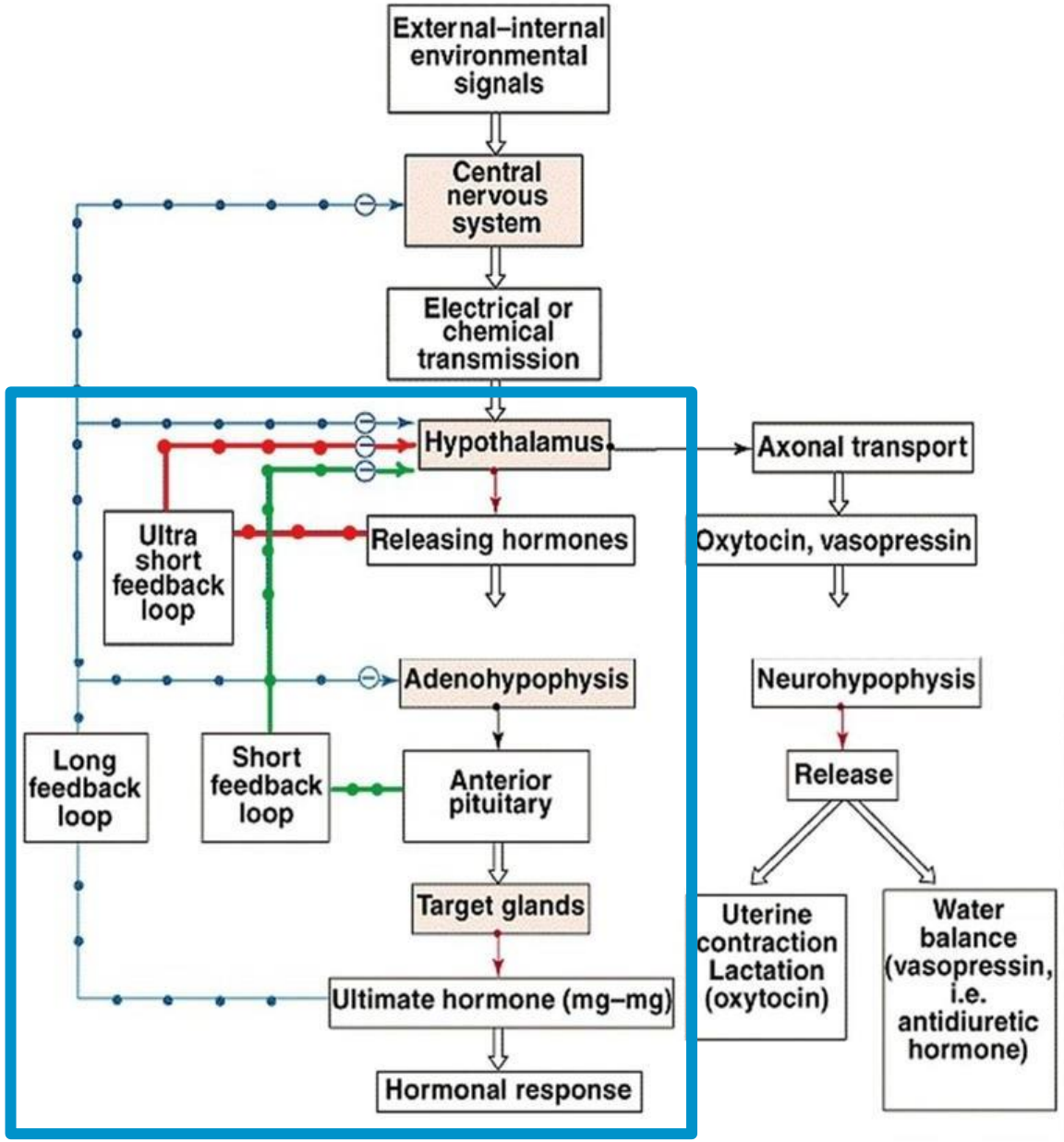
How the release is controlled?

- This diagram puts everything together.

1. We start with an **external or internal environmental signal**.
2. That signal is detected and processed by the **central nervous system**.
3. The CNS communicates through **electrical or chemical transmission** with the **hypothalamus**.
4. ***Then the hypothalamus has two major pathways :***

a) Pathway 1: Hypothalamus → anterior pituitary

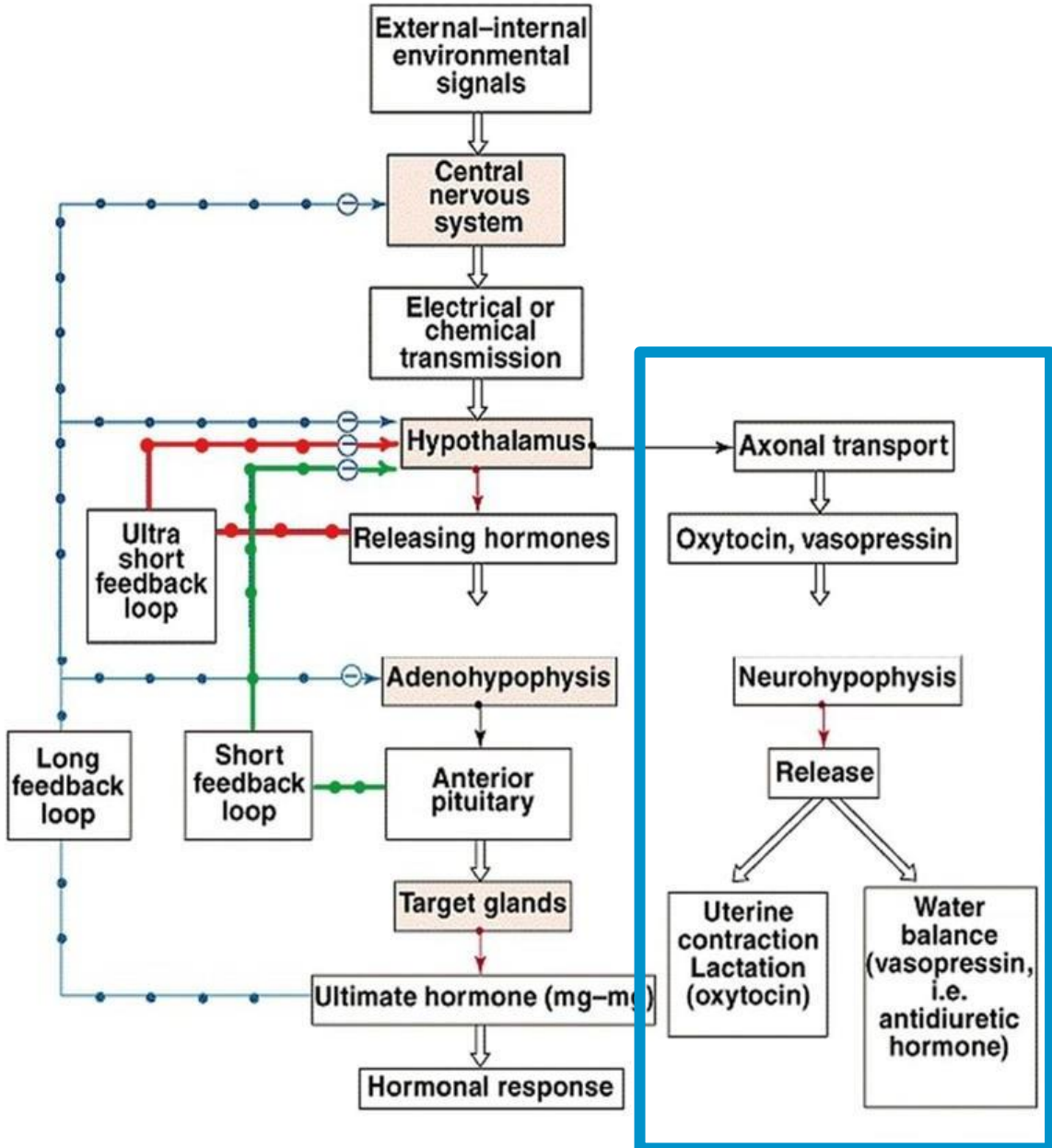
I. The hypothalamus produces **releasing hormones**.
II. These travel to the **adenohypophysis**, which is the **anterior pituitary**.
III. The anterior pituitary then releases hormones that act on the **target glands**.
IV. The target glands produce the **ultimate hormone**.
V. Finally, we get the **hormonal response**.
VI. And that ultimate hormone can provide **long negative feedback** back to the hypothalamus and pituitary.



How the release is controlled?

b) Pathway 2: Hypothalamus → posterior pituitary

I. There is another pathway shown on the right.
II. Some hormones are actually produced by neurons in the hypothalamus and transported down their axons to the **neurohypophysis**, which is the **posterior pituitary**.
III. The two important hormones here are:
IV. Oxytocin and **vasopressin (ADH).**
V. The posterior pituitary then releases them into the blood.
VI. Oxytocin → uterine contraction and lactation
VII. Vasopressin/ADH → regulation of **water balance**
VIII. So this pathway is different from the anterior pituitary pathway because the posterior pituitary mainly **stores and releases hormones made in the hypothalamus**.



Classification of hormones

- Chemistry, solubility, receptors' location, signaling mediator

  - ✓ **Small peptides, polypeptides and proteins**
  - ✓ **Amino acid derivatives and arachidonic acid analogs**
  - ✓ **Steroids**

Classification of hormones - Chemistry

Steroids

- Cholesterol-derived
- Transported by plasma proteins or specialized carrier (protection)

Small peptides, polypeptides, and proteins

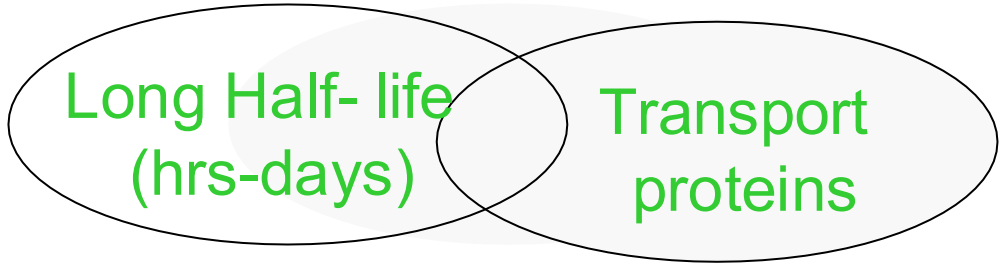
- Released and dissolve readily in blood and generally do not require special transport proteins.
- Most if not all polypeptides and proteins have specific carrier proteins

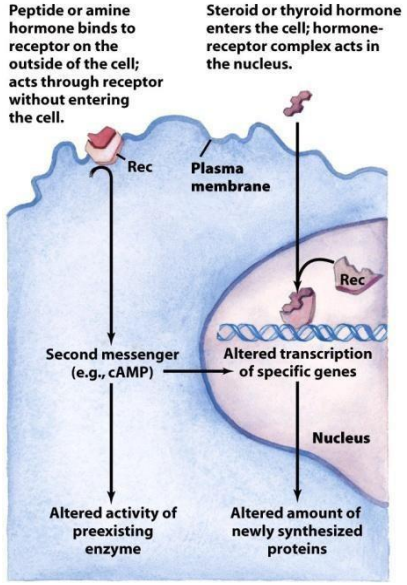
Amino acid derivatives and arachidonic acid analogs

- Catecholamines: released and dissolve readily
- Thyroid: bind transport proteins (prealbumin).

Classification of Hormones Mechanism of Action

- Hormones that bind to intracellular receptors **(lipophilic)**
  - Steroids
  - Thyroid hormones
  - Calcitriol, retinoic acid



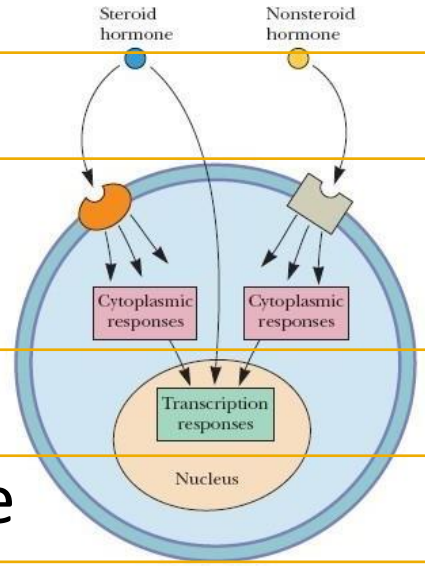


Classification of Hormones Mechanism of Action

- Hormones that bind to cell surface receptors **(lipophobic):**
- (According to **second messenger**):
  - **cAMP** (**β adrenergic factor, glucagon, ACTH**).
  - **cGMP** (**atrial natriuretic factor, Nitric oxide**)
  - **Calcium or phosphatidyl inositol** (**oxytocin,TRH**)
  - **Kinase or phosphatase cascade** (insulin, GH)

General features of hormone classes

	Group I	Group II
Types	Steroids, iodothyronines, calcitriol, retinoids	Polypeptides, proteins, glycoproteins, catecholamines
Action	Slow	Fast
Solubility	Lipophilic	Hydrophilic
Transport proteins	Yes	No
Plasma $t_{1/2}$	Long (hrs - days)	Short (minutes)
Receptor	Intracellular	Plasma membrane
Mediator	Receptor- hormone complex	cAMP, cGMP, Ca^{2+}, kinase cascades, metabolites of phosphoinositols



Genomic responses vs. rapid responses

TABLE 1-1 Nuclear Receptors and Involvement in Genomic and/or Rapid Biological Responses

(Steroid receptor) & ligand	# aa Receptor	Steroid nuclear receptors & gene transcription generate genomic responses (GR)	Steroid membrane receptors generates rapid responses (RR)
(Thyroid β) T_3	461	T_3 binding to its nuclear receptor, in target cells stimulates dissociation of co-repressors, recruitment of co-activators, etc. to complete a GR.	T_3 activates PI3kinases and MAP kinase **RR** pathways which can result in glucose uptake, Ca^{2+}-ATPase, Na^+/H^+ antiporter.
(Vitamin D receptor) 1α,25$(OH)_2$- vitamin D_3	427	Both intestinal Ca^{2+} absorption & kidney Ca^{2+} reabsorption requires **GR** for production of new calcium binding proteins (CaBP).	**RR** opening of Cl^- channels in osteoblasts & keratinocytes in 20 min; insulin secretion from β-cells, MAP kinase activation in NB4 cells.
(Estrogen receptor α) Estradiol	595	ERα **GR** are required for normal ovarian function.	ERα activates PI3K and then AKt **RR** stimulates nitric oxide NO.
(Estrogen receptor β) Estradiol	530	ERβ **GR** are required for ovulation & pregnancy.	The cell membrane ERβ bound to caveola has been implicated in RR.
(Glucocorticoid receptor) Cortisol	777	Knockout (KO) of the mouse GC receptor is lethal at time of birth.	Cortisol stimulates PI3-kinase/Akt to activate in seconds NO release.
(Mineralocorticoid receptor) Aldosterone	919	MR **KO** mice die of Na^+ and H_2O deprivation.	Aldosterone activates in 3–15 minutes the **RR** of Na^+/H^+ exchange in renal cells.
(Progesterone receptor) Progesterone	933	The progesterone receptor participates in **GR** sexual differentiation determination.	Progesterone stimulates **RR** within seconds to minutes, the acrosome reaction in spermatozoa.
(Androgen receptor) Testosterone	919	**KO** of the AR male mouse causes development of female genitalia.	Activation of MAP kinase then activates the ERK pathway via **RR**.

GR = genomic responses; RR = rapid responses. RR are not dependent on genomic responses. KO = Knock-out renders affected genes inactive.

Genomic responses vs. rapid Responses Gemini (Explanation)

Steroid and thyroid hormones act through two distinct signaling mechanisms: classic Genomic Responses (GR) mediated by nuclear transcription factors, and Rapid Biological Responses (RR) driven by membrane-associated signaling pathways.

Genomic Responses (GR): **Hormones cross the membrane to bind nuclear receptors,** displacing co-repressors and recruiting co-activators to directly alter gene transcription and protein synthesis.
Because GR requires mRNA transcription and translation, effects manifest over hours or days.
Gene knockout (KO) models highlight that GR pathways are vital for survival, systemic homeostasis, and structural differentiation.

Rapid Responses (RR): **Hormones bind membrane-bound receptors or subpopulations localized in caveolae.** These operate independently of gene transcription, acting within seconds to minutes by directly activating kinase signaling cascades (e.g., PI3K/Akt, MAP kinase/ERK), opening ion channels, or stimulating immediate downstream effects like nitric oxide (NO) release.
Key Examples by Receptor Thyroid Hormone (T_3, 461 aa): GR alters corepressor/coactivator complexes for genomic gene expression.

RR rapidly activates PI3K and MAP kinase, **directly increasing glucose uptake, Ca^{2+}-ATPase activity**, and Na^+/H^+ exchange.

Genomic responses vs. rapid Responses Gemini (Explanation)

Vitamin D ($1\alpha,25(OH)_2$-D_3, 427 aa): GR synthesizes **calcium-binding proteins (CaBP) for intestinal and renal Ca^{2+} absorption**. RR opens Cl^- channels in osteoblasts/keratinocytes within 20 minutes and triggers β-cell insulin secretion.

Estrogen (ERα 595 aa, ERβ 530 aa): GR drives ovarian development, ovulation, and pregnancy maintenance. RR activates PI3K/Akt to trigger rapid endothelial NO release (ERα) or acts through caveolae-bound receptors (ERβ).

Glucocorticoid (Cortisol, 777 aa): GR is indispensable for neonatal survival (GR KO is lethal at birth). RR stimulates PI3K/Akt to trigger NO release within seconds.

Mineralocorticoid (Aldosterone, 919 aa): GR prevents lethal salt and water wasting (MR KO causes death via Na^+ and H_2O loss). RR stimulates renal Na^+/H^+ exchange within 3–15 minutes.Progesterone (933 aa): GR guides embryonic sexual differentiation. RR triggers the immediate acrosome reaction in spermatozoa.

Androgen (Testosterone, 919 aa): GR is essential for male phenotype development (AR KO causes external female genitalia development in genetic males). RR activates MAP kinase to trigger downstream ERK signaling cascades.

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Harper’s Illustrated Biochemistry
2. Campbell’s Biochemistry

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slides 37	**Synthesis and release**	**'Synthesis and release' was deleted as they were written due to miss understanding that the hormones synthesis includes the 2nd messenger's written in the slide.**
V1 → V2			