# physiology

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◉ Sheet ○ Slides

Number

17

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## ***Introduction….***

Before we start talking about the synthesis and secretion of peptide hormones, I would like you to get familiar with some new terms such as prohormones, pre-hormones and pre-prohormones.

-***Prohormones***: precursor is a longer chained polypeptide that is cut and spliced together to make the hormone.

E.g. **Proinsulin** $\xrightarrow{\textbf{Cutting and splicing}}$ **Insulin**

-***Pre-hormones***: Molecules that are secreted by endocrine glands, which are inactive until they are changed to hormones in target cells.

E.g. **T4 (thyroxine)** $\xrightarrow{\textbf{Removal of 1 iodine}}$ **T3 (Triiodothyronine)**

-***Pre-prohormones***: Prohormone derived from larger precursor molecule

E.g. Pre-proinsulin

Note: we are just expected to know the previous Terms and their given examples

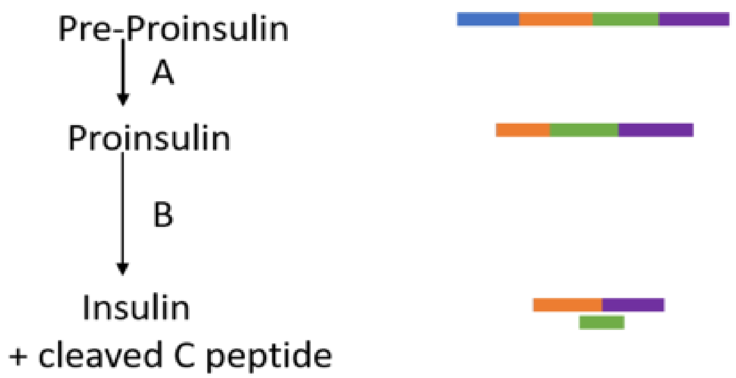



Figure 1: Progression of Insulin-like structures. A. The signal peptide of pre-proinsulin is cleaved, forming proinsulin. B) Proinsulin is folded in the ER, then transported to the Golgi apparatus where the C-peptide is cleaved using type I and type II endoproteases to form free C peptide and mature insulin.

signal peptide
B chain
C peptide
A chain

**Hormone's synthesis pass through several stages until we reach the final form of the hormone.**

# Synthesis and secretion of peptide and protein hormones

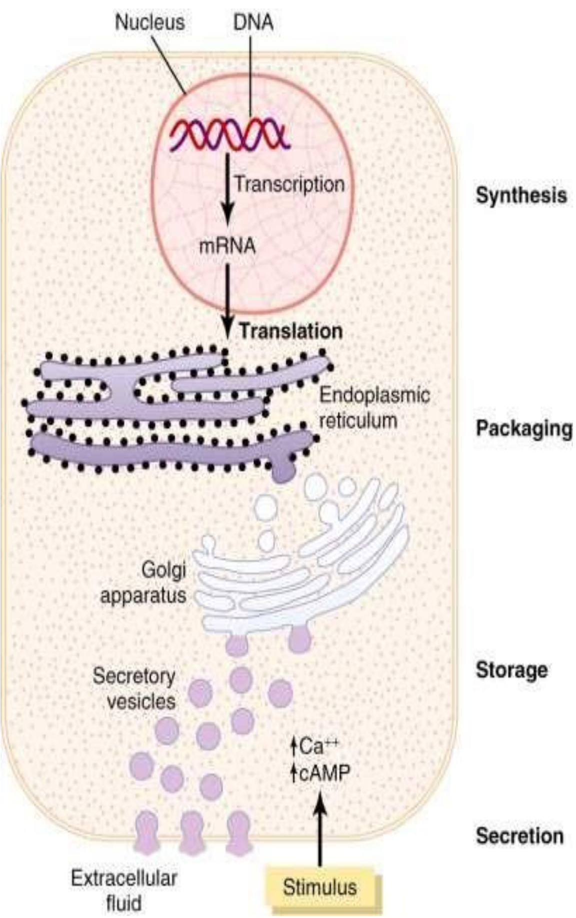
**Most of the hormones in the body are peptides and proteins. These hormones range in size from small peptides with as few as three amino acids (thyrotropin-releasing hormone) to proteins with almost 200 amino acids (growth hormone and prolactin).**

**Note that peptide hormones ≠ protein hormones ⇒ the basic distinguishing factor is size.**

**Polypeptide**

**Protein**: Polypeptide with 100 or more amino acids

**Peptide**: Polypeptide with fewer than 100 amino acids




i. ***Synthesis:*** *Protein and peptide hormones are synthesized on the rough end of the endoplasmic reticulum of the different endocrine cells. They are usually synthesized first as larger proteins that are not biologically active (preprohormones) and are cleaved to form smaller prohormones in the endoplasmic reticulum.*

ii. ***Packaging:*** These prohormones are then transferred to the Golgi apparatus for packaging into secretory vesicles. In this process, enzymes in the vesicles cleave the prohormones to produce smaller, biologically active hormones.

iii. ***Storage:*** *The vesicles are stored within the cytoplasm, and many are bound to the cell membrane until their secretion is needed.*

iv. ***Secretion:*** The secretion of hormones takes place by *exocytosis.*

*The figure **above** shows the synthesis and secretion of peptide hormones. The stimulus for hormone secretion often involves changes in intracellular calcium or changes in cyclic adenosine monophosphate (cAMP) in the cell.*

**QUESTION**: Is it possible to have an inactive hormone although it is in its final for?

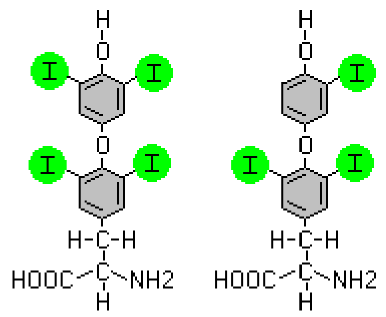
**Yes it is**. In some cases, the molecule secreted by the endocrine gland (and considered to be the hormone of that gland) is actually inactive in the target cells. In order to become active, the target cells must modify the chemical structure of the secreted hormone. Thyroxine (T4), for example, must be changed into T3 (*Triiodothyronine)* within the target cells in order to affect the metabolism of these cells.

**Thyroid hormones**

- *Thyroxine (T4): Inactive form of the thyroid hormone.*
- *Triiodothyronine (T3): Active form of the thyroid hormone.*

BOTH are synthesized & secreted by the "thyroid gland"

Despite the fact that (T3) is the active form of the thyroid hormone, the major form of thyroid hormone in the blood is thyroxine (T4).Therefore, ***thyroxine*** hormones are converted into ***Triiodothyronine*** hormones *by the removal of an iodine atom.*

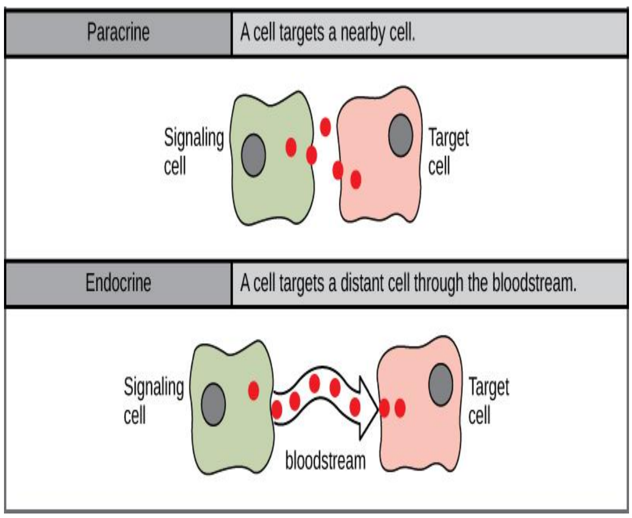


Thyroxine (T4) Triiodothyronine (T3)

## Endocrine hormones vs. Paracrine hormones

- ***Endocrine hormones***-Travel through the blood to act at a site distant from the secreting cell or gland.
  I. Amino acid derivatives.
  II. Peptides.
  III. Proteins.
  IV. Steroids.

- ***Paracrine hormones***-Act on cells near the secreting cell.
  I. Amino acid derivative.
  II. Arachidonic acid (fatty acid) derivative.



**Note: "The table below has to be memorized".**

**Doctor Ebaa said: "This table is here to help you memorize hormones".**

**Table 10-4 Chemical Classification and Function of Hormones**

| Chemical Classification | Examples | Regulated Function |
|---|---|---|
| **Endocrine Hormones** | | |
| Amino acid derivatives | Epinephrine (adrenaline) and norepinephrine (both derived from tyrosine) | Stress responses: regulation of heart rate and blood pressure; release of glucose and fatty acids from storage sites |
| | Thyroxine (derived from tyrosine) | Regulation of metabolic rate |
| Peptides | Antidiuretic hormone (vasopressin) | Regulation of body water and blood pressure |
| | Hypothalamic hormones (releasing factors) | Regulation of tropic hormone release from pituitary gland |
| Proteins | Anterior pituitary hormones | Regulation of other endocrine systems |
| Steroids | Sex hormones (androgens and estrogens) | Development and control of reproductive capacity |
| | Corticosteroids | Stress responses; control of blood electrolytes |
| **Paracrine Hormones** | | |
| Amino acid derivative | Histamine | Local responses to stress and injury |
| Arachidonic acid derivatives | Prostaglandins | Local responses to stress and injury |



## ***Notes about the previous table:***

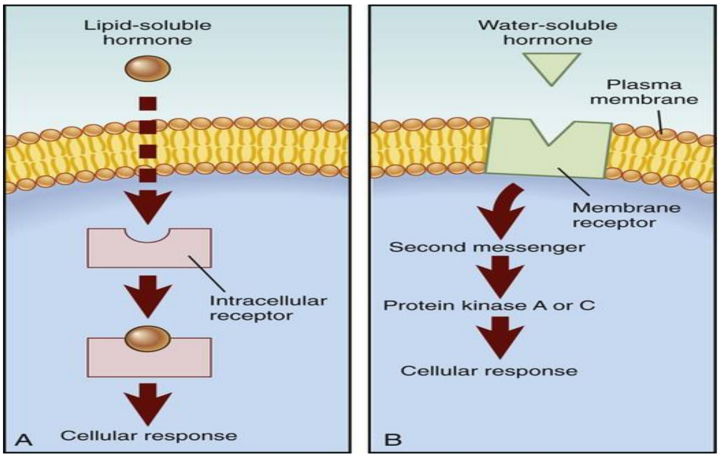
- Paracrine hormones are considered **inflammatory mediators**. Histamine, for example, is a chemical mediator which is released from cells during inflammation triggering vasodilation and increasing vascular permeability.
- Dopamine, in most cases, acts as a ***neurotransmitter.*** It might also act as a ***neurohormone*** "amine derivative hormone".
- Epinephrine and norepinephrine are water soluble hormones, meanwhile, T3 and T4 are Lipid soluble hormones.
- All the anterior pituitary hormones are ***proteins***.
- All the hypothalamic hormones are ***peptides***.
- ***Androgen*** hormones are sex hormones produced by the adrenal cortex. Therefore, they are examples on ***adrenocortical hormones***
- ***Adrenocortical hormones*** are hormones produced by the adrenal cortex, the outer region of the adrenal gland.
- ***Steroid hormones are lipid soluble hormones.***

# Lipid Soluble hormones vs. Water Soluble Hormones

**The *solubility* of a hormone correlates with the location of the receptors inside or on the surface of target cells.**

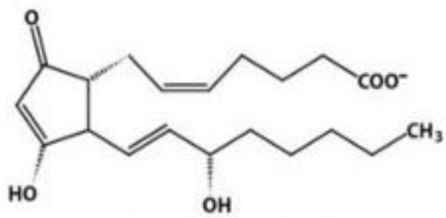
a) Water soluble hormones have their receptors on the surface of the target cells
b) Lipid soluble hormones have their receptors within the nucleus (and sometimes within the cytoplasm) of the target cells.

***The figure beside illustrates the differences between the lipid soluble hormones and the water soluble hormones.***




Prostaglandin hormones are arachidonic acid "fatty acid" derivatives and therefore are expected to be classified in the lipid soluble hormones. Are they?

❖ Unexpectedly, prostaglandin hormones are classified in the "water soluble hormones" **category** and that is due to the presence of a very small charge at the end of the compound which prevents it from crossing the hydrophobic membrane.




**Prostaglandin $E_2$**

**Note**: According to Dr. Ebaa prostaglandin hormones are lipophilic but they bind to the cell surface receptors of the target cell and that is the reason behind classifying them as "water soluble hormones".

## ❖ Peptide & Protein Hormones

| Gland/Tissue | Hormones | Gland/Tissue | Hormones |
|---|---|---|---|
| Hypothalamus | • TRH, GnRH, CRH GHRH, Somatostatin, | Placenta | • **HCG, HCS, 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 |
| Pancreas | • Insulin,Glucagon, Somatostatin | | |
| Liver | • Somatomedin C (IGF-1) | Adipocyte | • Leptin |
| Parathyroid | • PTH | Adrenal medulla – Epinephrine, Norepinephrine | |

**Dr. Ebaa said**: "you are supposed to know the peptide and protein hormones (summarized in the table above) and that they have membrane receptors on the surface of the target cells".

***Hypothalamus*** **secretes** the "releasing hormones" which are:

***1) TRH: Thyrotropin-Releasing Hormone.***

***2) GnRH: Gonadotropin-Releasing Hormone.***

***3) CRH: Corticotropin-Releasing Hormone.***

***4) GHRH: Growth Hormone-Releasing Hormone.***

***5) Somatostatin: growth hormone inhibitory hormone***.

***Anterior pituitary*** **secretes** the following hormones:

***1) ACTH: Adrenocorticotropic hormones***

***2) TSH: Thyroid-Stimulating Hormone.***

***3) FSH: Follicle-Stimulating Hormone.***

***4) LH: Luteinizing Hormone.***

***5) GH: Growth Hormone.***

***6) PRL: Prolactin.***

## ❖ ***Amine Hormones***

- Hormones derived from the modification of amino acids (tyrosine).
- Examples include: 1) Dopamine.

  2) Epinephrine & norepinephrine (EPI, NE).

  3) T3 & T4.

***Hypothalamus*** → *Secretes* → **Dopamine.**

***Thyroid*** → *Secretes* → **T3 & T4.**

***Adrenal medulla*** → **Secretes** → ***Epinephrine & norepinephrine***.

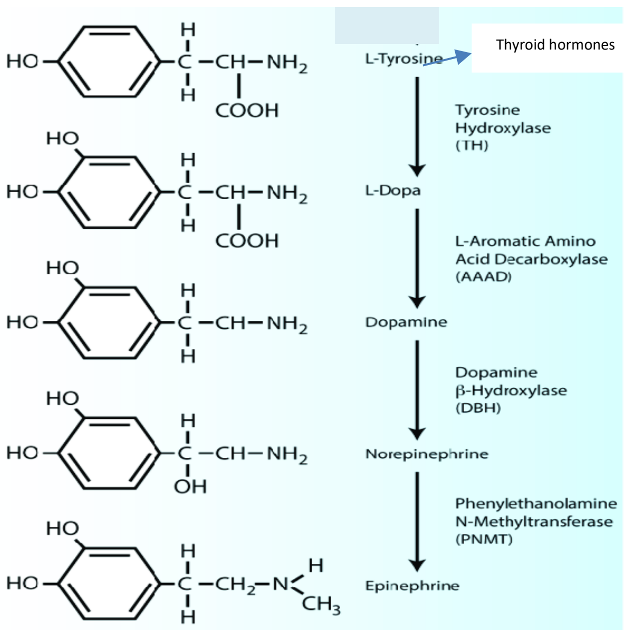
# Synthesis of Amine Hormones:

The figure below emphasizes the fact that tyrosine is the source for amine hormones.

All of this pathway depends on the availability of enzymes and the main source "tyrosine".

So let us say that we had tyrosine, TH (enzyme) and AAAD (enzyme) then we would end up with dopamine hormone. Notice that the absence of DBH (enzyme) impedes (prevents) the formation of norepinephrine and so epinephrine.

Thyroid gland has enzymes that play a role in the synthesis of thyroid hormones.




Note: Refer back to slide "7".

Note that the chemical structures above are just for **clarification**.

❖ ***Steroid Hormones***

| Gland/Tissue | Hormones |
|---|---|
| Adrenal Cortex | ▪ Cortisol, Aldosterone, Androgens |
| Testes | ▪ Testosterone |
| Ovaries | ▪ Estrogens, Progesterone |
| Corpus Luteum | ▪ Estrogens, Progesterone |
| Placenta | ▪ Estrogens, Progesterone |
| Kidney | ▪ 1,25-Dihydroxycholecalciferol (calcitriol) |

Note: Dr. Ebaa did not mention anything new about the previous table. She only listed them and said that these steroid hormones represent the most crucial ones in our body.

The table below summarizes the different types of hormones based on their ***chemical structure.***

***Note: We are not expected to know all the details in the table below as they will be discussed later on.***

| | Peptide | Steroid | Amino acid derivative |
|---|---|---|---|
| **Synthesis** | Synthesised as **prohormones**, requiring further processing (e.g. cleavage) to activate | Synthesised in a series of reactions from **cholesterol** | Synthesised from the amino acid **tyrosine** |
| **Storage** | Stored in vesicles (regulatory secretion) | Released immediately (constitutive secretion) | Stored before release (storage mechanism varies) |
| **Solubility** | Most are polar and water soluble, can travel freely in the blood | Generally non-polar and require carrier proteins to travel in blood | Some are polar (adrenaline), others must be protein-bound |
| **Receptors** | Bind receptors on cell membrane and transduce signal via the use of second messenger systems | Bind to intracellular receptors to change gene expression directly | Adrenaline acts on membrane receptors, while thyroid hormones act directly on nuclear receptors |
| **Effects** | Often fast onset transient changes in protein activity, though gene expression changes can occur | Alterations in gene expression; slower onset but longer duration than peptide hormones | Adrenaline functions like peptides, thyroid hormones function in a similar manner to steroids |
| **Examples** | Insulin, glucagon, prolactin, ACTH, gastrin parathyroid hormone | Cortisol, aldosterone, estrogen, progesterone, testosterone | Adrenaline, thyroxin, triiodothyronine |

## ✓ Hormone activity:

The first step of a hormone's action is to bind to specific receptors at the target cell. Therefore, cells that lack receptors for the hormones do not respond.

| |
|---|
| *Do we always have a constant number of receptors on the cell membrane or within the cytoplasm (including the nucleus)?* |

**Absolutely no**. The number of receptors in a target cell usually **does not** remain constant from day to day or even from minute to minute. Receptor proteins are often inactivated or destroyed during the course of their function, and at other times they are reactivated or new ones are manufactured by the cell, and that is why receptors are considered to be dynamic.

***The number and sensitivity of hormone receptors are regulated in two different ways:***

- ***Up-regulation (priming effect)*:** The mechanism in which a hormone increases the number or affinity of its receptors causing the target tissue to become progressively more sensitive to the stimulating effects of the hormone.
    - **Up-regulation might take place by :**
        1) Increasing the number of receptors formed on target cells in response to particular hormone
        2) **Triggering the inactivated receptors (switching them on) so we have a greater availability of the receptor for interaction with the hormone (**Greater response by the target cell).

- ***Down-regulation (desensitization):*** The mechanism in which a hormone decreases the number or affinity of its receptors and that is when the cell is stimulated for a long period of time causing the target tissue to become less responsive to the hormones.
    - **Down-regulation mainly takes place by lowering the number of activated receptors.**
    - **Pulsatile secretion (to avoid the secretion of large quantities of a specific hormone for a long time) may prevent downregulation.**

## ***Notes***:

- *Unexpectedly,* prolonged exposure to high hormone concentrations can decrease the number of receptors of that hormone; desensitizes the target cells, so they response less vigorously (potently) to hormonal stimulation, preventing them from overreacting to persistently (continuously) high hormone levels.
- Pregnant women for example undergo upregulation. As pregnancy hormones move through the body, cellular changes occur to prepare for delivery. Cells in the ***uterus*** become more sensitive to ***oxytocin*** which in turn leads to the contraction of the uterus. This example is just to make sure that we understand the meaning of up-regulation.

## ***Concentrations of Hormones in the Circulating Blood***

*Two factors can increase or decrease the concentration of a hormone in the blood. One factor is the* ***rate of hormone secretion into the blood****. The second is the* ***rate of removal of the hormone from the blood****, which is called the* ***metabolic clearance rate*** *and is usually expressed in terms of the number of millilitres of plasma cleared of the hormone per minute.*

- Note: Different hormone concentrations can have different physiological responses despite having the exact same ligand and receptor.

**Half-life:** The time required for the blood [hormone] to be reduced to ½ reference level.

According to ***half-life***, hormones are classified into:

1. Hormones with long half-lives (~~ hours-days~~): steroids and thyroid hormones.
2. Hormones with short half-lives (~~minutes~~): peptides and catecholamines.

***Notes***:

- ✓ Reference level is the original amount of hormone that was secreted.
- ✓ Catecholamines are dopamine, epinephrine and norepinephrine.

## Affinity of receptors to ligands, Kd:

Affinity of receptors represents the strength of binding between the receptor and ligand, and it can be calculated by **Kd**.

**-**Kd is the disassociation constant which relates inversely to the affinity.

**-**In other words, the higher Kd is, the lower the affinity of the receptor, and vice versa.

**Important example for understanding:**

Let's say you have 2 receptors in your body, receptor (A) has a high affinity for Ach and receptor (B) has a low affinity for Ach, then a lower concentration of Ach at receptor (A) than (B) can give the same physiological response. In other words, if we put 60% Ach next to receptor (B) then to produce the same physiological response at receptor (A) we need less than 60% Ach because it has higher affinity (better interactions).

## ✓ Mechanisms of hormone action:

**-**Hormones of same chemical class have similar mechanisms of action, those similarities include:

**1)** ***Location*** of the cellular receptor proteins depends on the chemical nature of the hormone.

**2)** ***Events*** that occur in the target cell.

**3)** The response of the receptor to a hormone depends on the ***specific binding*** between the ligand and the receptor.

**4)** Hormones exhibit ***affinity*** (bind to receptors with high bond strength) and ***saturation*** (low capacity of receptors).

**5)** Response depends on both the ***hormone*** and the ***target cell***, so having the same ligand and receptor within different cells can cause different physiological responses. E.g. same ligand and receptor in bronchioles cause constriction but in smooth muscles of blood vessels it causes dilation of blood vessels.

**6)** ***Lipid soluble*** hormones bind to receptors ***inside*** the cell while ***water soluble*** hormones bind to receptors ***on the surface*** of the cell.

**7)** Responsiveness of target cell depends on the ***concentration*** of the hormone and on the ***abundance*** of target cell receptors.

**8)** Activation of receptors on the membrane of target cells causes activation of ***second messenger system*** and ***amplification*** of original small signal.