ENDOCRINE SYSTEM

Pharmacology

Lec. 1

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Endocrine Pharmacology

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Welcome back to pharmacology again! 💊

This lecture would **not** be hard since it only covers the basics. You'll see explanations for anything unclear, but in the end, make sure to focus on the content of the original slides. Keep your energy up and let's start!

The doctor began the lecture by reminding you that you are now familiar with his teaching style from the introductory course. His question's level and manner are typical now, nothing out of the ordinary. This lecture will be an introduction; however, it is very important as it will provide an overview of Endocrine Pharmacology. Attendance is highly important!

These are the names of all lectures in our course:

1. Introduction and hormone receptors
2. Pharmacology of hypothalamic and anterior pituitary hormones
3. Pharmacology of thyroid hormones (recorded)
4. Pharmacology of parathyroid gland (recorded)

They'll be uploaded on the weekend, maybe on Thursday

5 & 6. Pharmacology of adrenal gland hormones

7 & 8. Pharmacology of pancreatic hormones

"if you studied the slides and attended the lectures ,I promise the questions will be straightforward ,believe me, very very easy"

-القائل: دكتور سهيل

- **General ILO'S**

- **Available preparations and their pharmacological properties: pharmacodynamics and pharmacokinetics**
- **Mechanism of action: how hormones mediate their effects**
- **Clinical uses**
- **Major side effects**

Colors Code:

Red color in slides refers to Dr speech during the lecture

Any box marked with  this star means it's additional information for ur better understanding , not from Dr

Remember to focus on slides themselves!

Basic principles

- Endocrine Pharmacology vs Endocrine Physiology
- 2nd in importance after CNS.
- Endocrine System

- Uses chemical signals (hormones) for cell to cell communication
- Coordinates the function of cells
- Response to an endocrine signal occurs within minutes to hours (ductless glands) and hormones are secreted in very small amounts, they're stored in glands and released when needed.

- Most of what the doctor is explaining has been previously explained in physiology, biochemistry, and anatomy lectures. This is, after all, an introductory lecture.

- There is no sharp difference between endocrine pharmacology and physiology because most hormones are synthesized in specific glands inside the body normally, but in Pharmacology we are going to use hormones as drugs with their therapeutic level and so on.

- The CNS is considered more important because it has most regulatory centers, however there are intersections between the two systems such as in the hypothalamus (which is part of the CNS) that secretes hormones into the posterior pituitary and also releases hormones for regulation of the anterior pituitary's secretion. Moreover, drugs, toxins, environmental factor which affect the CNS could also affect the Endocrine system, and vise versa. (This paragraph isn't very important)

- **Hormonal regulation ↑↓ these arrows means that hormones might be stimulatory or inhibitory**

- Growth & development

- Reproduction, fertility, sexual function

- Response to environmental situations (stress…)

- Maintenance of normal homeostasis

As you know, hormones play a crucial role in regulating various physiological processes:

- **Growth & Development:** Hormones like growth hormone (GH) and thyroid hormones are essential for proper growth and development of tissues and organs.
- **Reproduction, Fertility, and Sexual Function:** Hormones such as estrogen, progesterone, and testosterone regulate reproductive processes and sexual functions.
- **Response to Environmental Situations:** Hormones like cortisol are involved in the body's response to stress and other environmental changes.
- **Maintenance of Normal Homeostasis:** Hormones help maintain internal balance (homeostasis) by maintaining components of extra-cellular fluid, and regulating processes such as metabolism, blood pressure, and fluid balance

Don’t forget that this star means it’s additional information

- **Hormones**

- Chemical substances synthesized in and released from highly specialized cells collectively known as Endocrine glands, immediately secreted into blood stream and act at some other place

- Considered cell to cell communication molecules

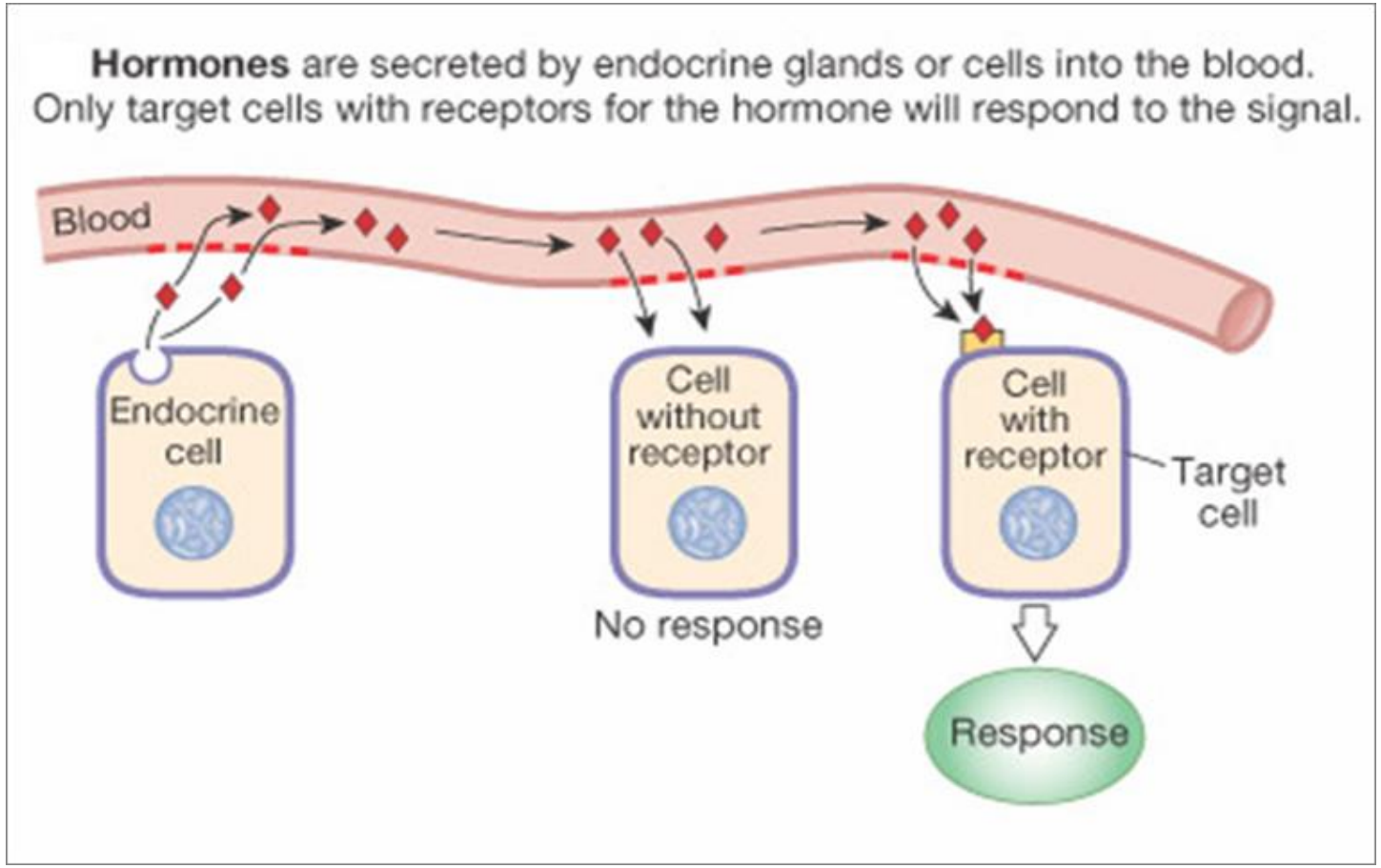
- Transported by blood

- Distant or local target tissue receptors it binds to specific receptors - Activates physiological response " the effect "

- **Cell-to-Cell Communication: Hormones facilitate communication between cells.**
- **Transport: They are carried by the blood to various target tissues.**
- **Target Receptors: Hormones act on specific receptors located either at distant or local tissues.**
- **Physiological Response: Their binding to these receptors triggers specific physiological responses in the body.**

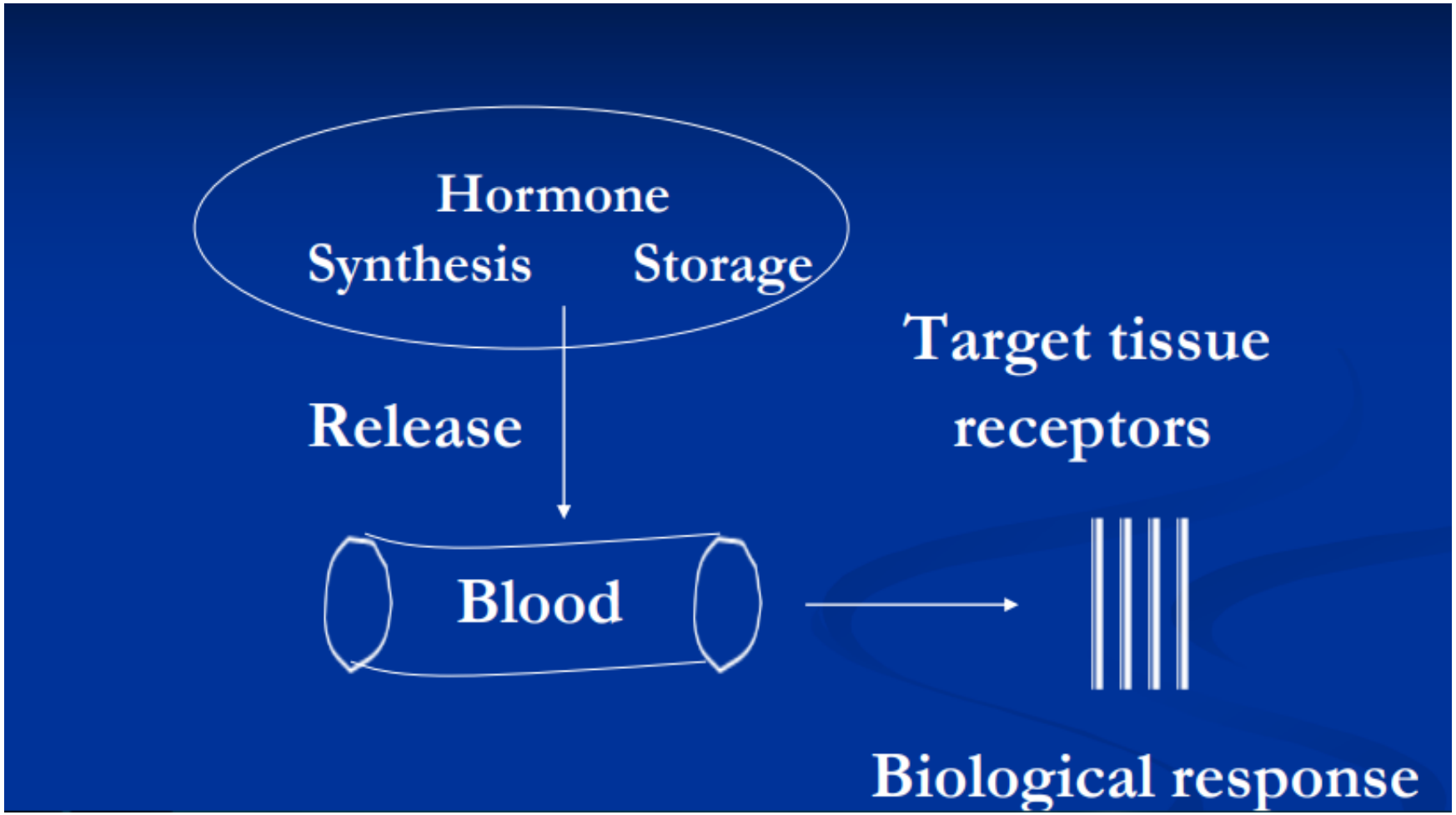
❗ Example for this cascade:

Hypothalamus (CRH) → Pituitary Gland (ACTH) → Adrenal Glands (Cortisol) → Target Tissues → physiological response



- **Hormones, whenever they are needed, are released in the bloodstream by endocrine gland and the cell which contains specific receptor to this specific hormone will mediate the effect, whereas the tissues which lack such receptor will have No effect**

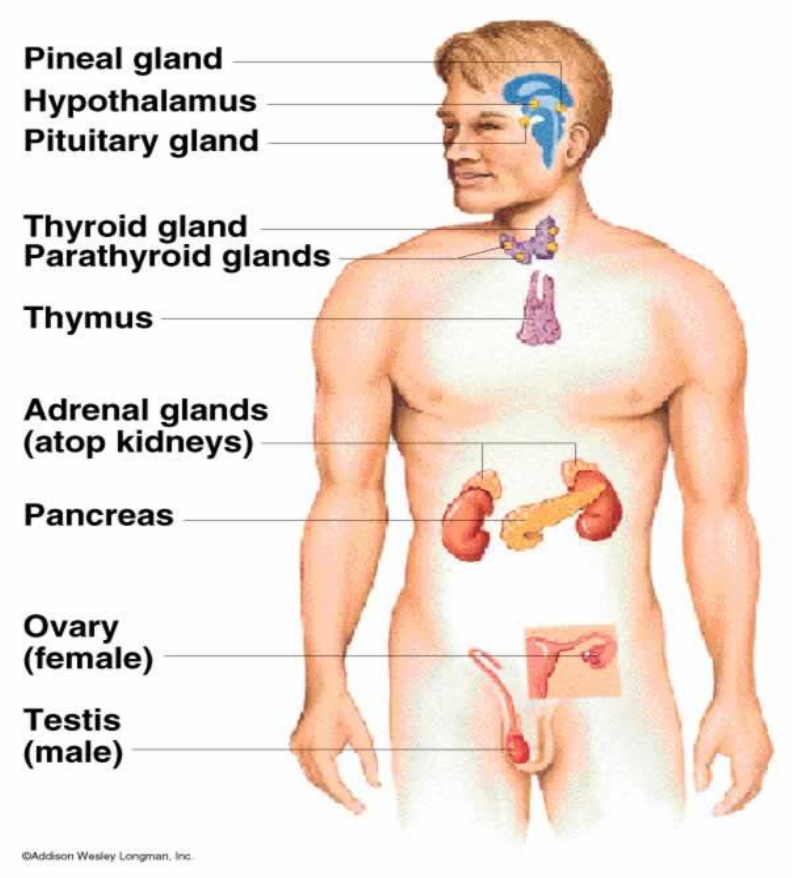
Same as previous



- **Glands:**

Hypothalamus
Pituitary
Thyroid
Parathyroid
Pancreas
Adrenals
Ovaries
Testes

not in this course, later, in 3rd year



- **Chemical nature of hormones**

- **Amino Acid derivatives:**

  T3, T4 Thyroxine, Dopamine (precursor=Tyrosine)

- **Small peptides; polypeptides; large proteins or glycoproteins:**

  Hypothalamic hormones, GH, PRL, Insulin, Glucagon, LH, FSH, TSH…

- **Steroids: all are synthesized from cholesterol**

  Cortisol, Aldosterone, Estrogen, Progesterone, Androgens…

- **Amine Hormones**

- Derived from the amino acid Tyrosine

- Include the Catecholamine Dopamine & Thyroid hormones

- They are stored until secreted

*** Receptor locations:**

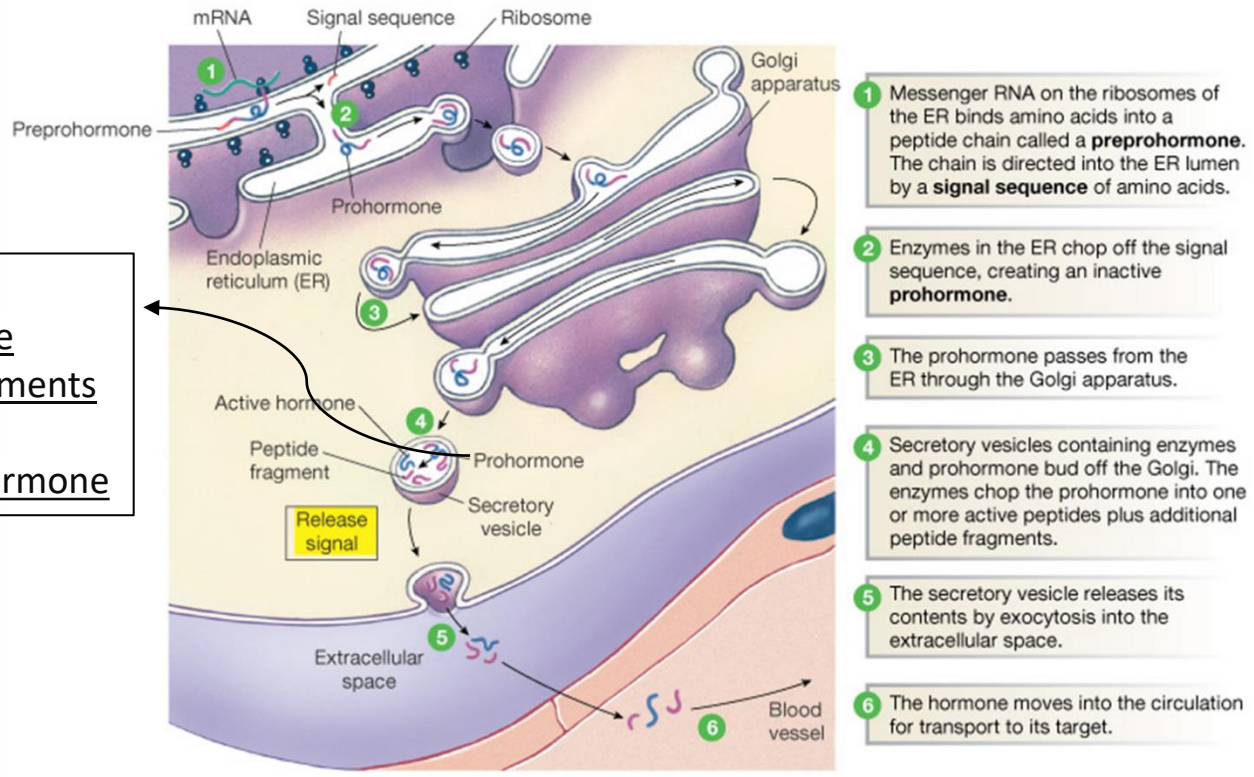
- Surface (Dopamine)

- Intracellular (nuclear; T_3 & T_4) مهمة

- The doctor is reading through these slides normally while adding a few words here and there. Don't worry, you are not missing anything important! Study the slides and you should be fine.

Protein and Polypeptide Hormones: Synthesis and Release

Additional info to not get confused
Vesicles contain both the newly formed active hormones and any residual prohormone fragments that may not have been fully converted.
But of course it contains ***mainly*** the active hormone



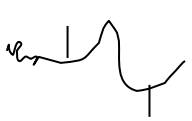
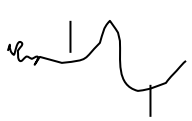
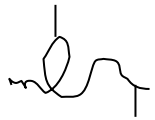
Preprohormone → Prohormone → Hormone → In vesicles → Released to bloodstream → Reach target cell → Interact with specific receptor

ER Golgi

*** some hormones such as insulin and PTH have large precursors :e.g pre-pro-parathyroid hormone (PreProPTH)**

الدكتور شرح يلي فوق بس بالآخر حكا انه هاي أهم معلومة وهاد يلي بده اياك تعرفه:

Some hormones come from large precursors(pre pro), which can be used clinically .Also, we have synthetic machinery for hormones , this machinery contains enzymes and these enzymes can be *targeted* by the drugs; either being agonists, or antagonists to inhibit synthesis for this hormone.

	LH	FSH	TSH	hCG
α				
β				

- All these above are glycoproteins composed of Alpha and Beta subunits. As you can see the alpha subunit is similar meaning that it comes from the same single gene, while the beta is from different genes, which explains why it's responsible for the different functions they deliver.

  How did they know that the beta is responsible for function?

- For example, -على سبيل المثال لا الحصر-they combined the alpha glycoprotein from LH with the beta glycoprotein from TSH they found that Glycoprotein acted on the Thyroid and not on Gonads. (TSH not LH effect)

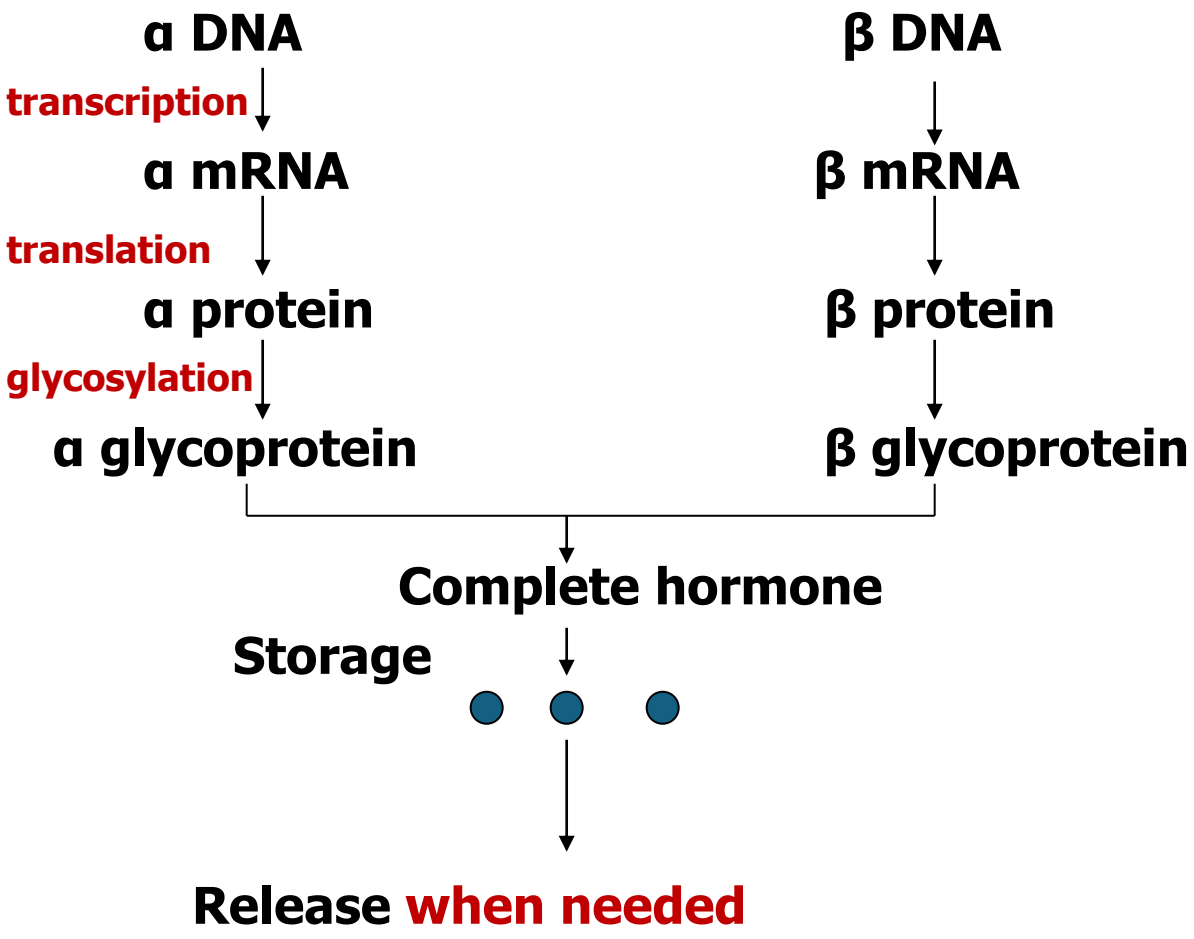
- Let's get to know the meaning of the prev. slide – it's related more to Biochemistry, so you can only read it to refresh previously learnt information, not for memorization 👀:

- All the previous hormones are heterodimeric proteins, meaning they are composed of two different subunits (α and β), each with a specific structure and function.

- The α subunit is identical among these hormones, while the β subunit is unique and confers the specific biological activity to each hormone.

- The α subunit in LH, FSH, TSH, and hCG is structurally the same, it plays a role in the proper folding and stability of the hormone, but it does not determine the hormone's specific function.

- While The β subunit varies among them. This variation is crucial because it determines the receptor specificity and biological function of each hormone. These unique β subunits interact with distinct receptors on target cells, eliciting specific physiological responses.



- Understanding the synthetic machinery of hormones (whether they are glycoproteins or not) is clinically important when it comes to treating patients that have certain disorders relating to these hormones, because we could understand which stage is defective and/or we could target a stage to exploit for drug-mediated regulation for managing these disorders.

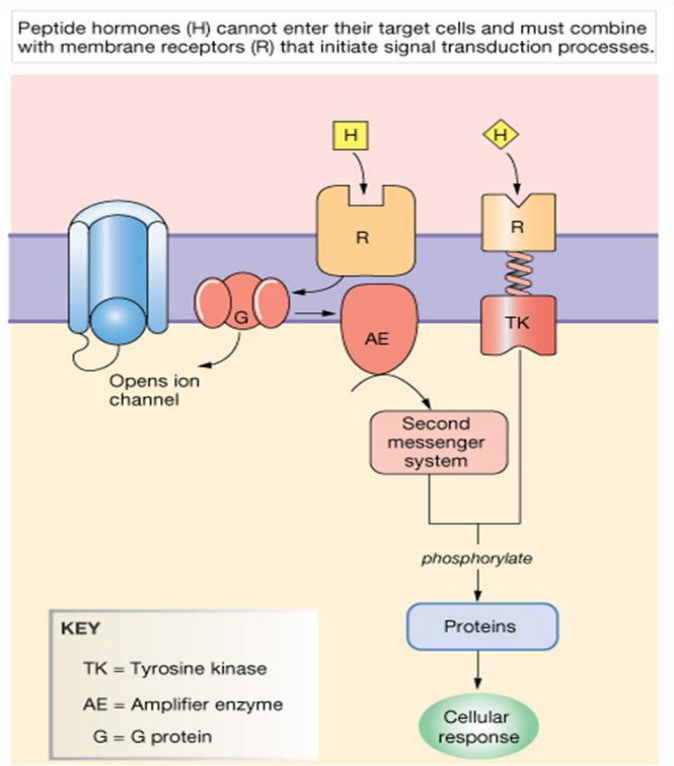
- For example, we could use drugs that agonize a specific stage of hormone synthesis to treat patients with deficiency of that hormone. Or we could antagonize those stages for patients with an overproduction of that hormone.

- The steps of releasing hormones from their respective storage pools are important stages of regulation as well:

- For example, Anti-Thyroid drugs function by inhibiting hormone synthesis, which results in a delayed onset of action because the process of synthesis takes time. In contrast, other drugs may target the release of hormones, leading to quicker effects since they act directly on the final step (releasing) before the hormone enters circulation.

Protein and Polypeptide Hormone Receptors

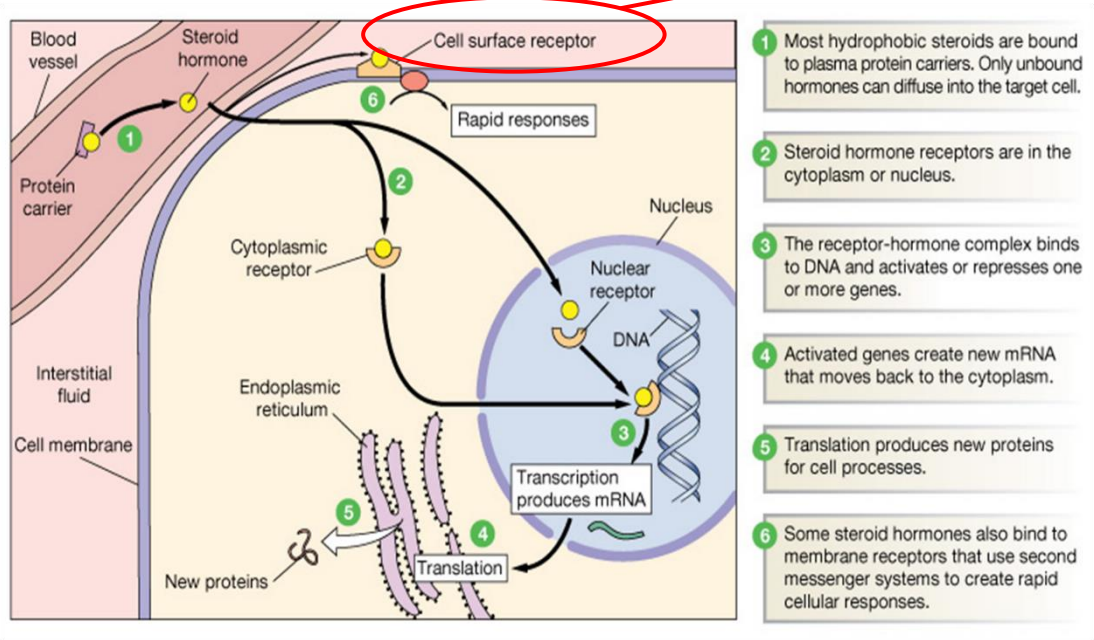
- **Bind to surface receptor such as Dopamine**
- **Transduction**
  - **System activation such as G-Protein**
  - **Open ion channel**
    - **Enzyme activation such as kinases**
    - **Second messenger systems**
    - **Protein synthesis**



- **Professor didn't explain this picture**

Steroid Hormones Receptors

For exam purposes the main place for the steroid receptor is <u>intranuclear</u> , <u>not on surface</u>

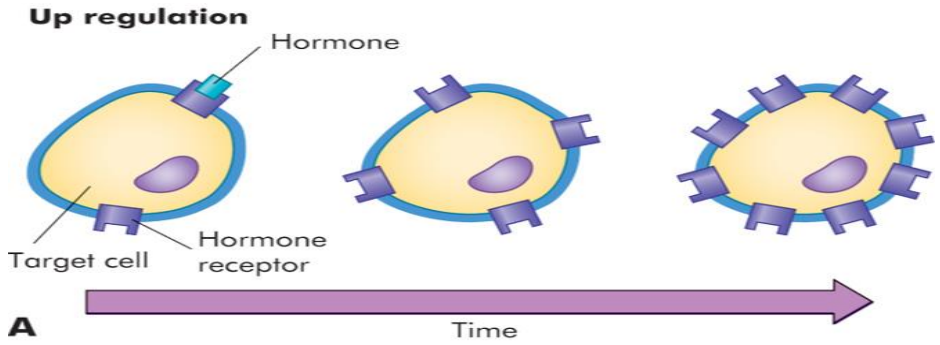


- **These steroid hormones must be very lipid soluble to pass through the nuclear membrane which is very tough and hard to pass.**

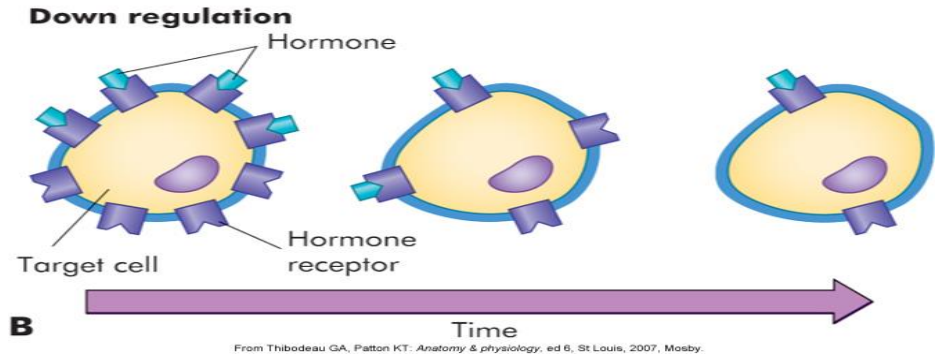
Hormones cascade:

- **Synthesized by specific glands → Bind to specific proteins (carriers) in the blood → Reach the target cell → Interact with the specific nuclear receptor → Elicit a response**

Hormone receptors are subject to 2 important phenomena



1- Sensitization: <u>increase</u> number of receptor on Target cell.
e.g. : drugs to treat DM2



From Thibodeau GA, Patton KT: *Anatomy & physiology*, ed 6, St Louis, 2007, Mosby.

2- Desensitization: <u>decrease</u> number of receptor On Target cell
e.g: insulin receptors in DM2 (insulin resistance)

- **Basal conditions...minimal release, will not exceed 10^{-13} – 10^{-9} molar concentration**

- **Stimuli: such as prolactin levels in pregnancy for lactation or Cortisol in stress situation. Stimulus could be by:**

1- Nerve impulse

2- Change in composition of ECF

- " إذا أكلت وقيّة كنافة شو رح يصير بمستوى الانسولين؟ رح يزيد نتيجة لهذا المحفز "

3- Another hormone (trophic hormone)

blood → target cells → receptors → initial change → cascade of reactions → recognizable change...

What could this recognizable change be? If it was insulin it will increase cells permeability for glucose, there are other changes such as:

- Change in cell permeability

- Stimulation or inhibition of protein synthesis

**** Transcription or translation**

- Stimulation or inhibition of mediator release

(second messenger)

**** cAMP; DAG; Ca^{++} ; ITP (IP_3)...**

The following is additional explanation:

- **Minimal Release:** Under basal conditions, the endocrine glands release a minimal amount of hormones to maintain basic physiological functions. This ensures that the body maintains homeostasis even without external stimuli.

- **Nerve Impulse:** Neural signals can stimulate hormone release. For example, Hypothalamic-Pituitary Axis: The hypothalamus receives nerve signals and responds by producing releasing or inhibitory hormones that act on the pituitary gland, which then secretes hormones that affect other endocrine glands.

- **Change in Composition of ECF (Extracellular Fluid):** Changes in the levels of ions, nutrients, or other substances in the extracellular fluid can trigger hormone release. For instance, an increase in blood glucose levels stimulates the pancreas to release insulin.

- **Another Hormone (Trophic Hormone):** Hormones that regulate the release of other hormones are called trophic hormones. For example, Thyroid-Stimulating Hormone (TSH) from the pituitary gland stimulates the thyroid gland to release thyroid hormones.

- **How long a hormone stays high in blood?**

Depends on:

- Extent of protein binding

- Efficiency of degradable enzymes & clearance

Metabolism & excretion

- <u>Efficiency of negative feedback mechanisms</u> مهمة

The following is additional explanation:

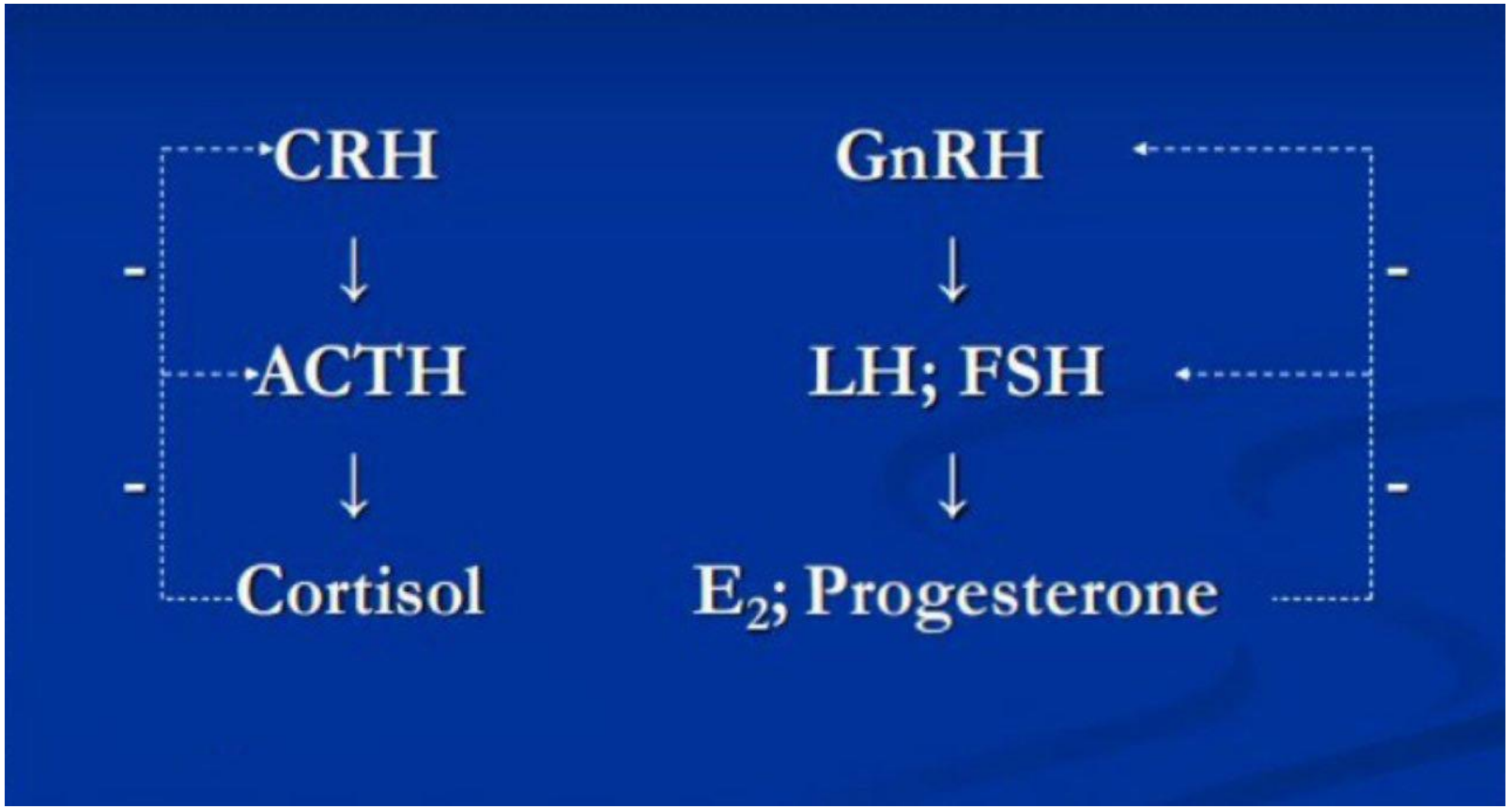
1.Extent of Protein Binding: Hormones that bind extensively to plasma proteins tend to stay in the bloodstream longer because the binding decreases their rate of clearance.

2.Efficiency of Degradable Enzymes and Clearance: Hormones are broken down by enzymes such as in liver and elsewhere. Efficient enzyme activity leads to faster metabolism and shorter hormone presence in the blood.

3.Metabolism and Excretion: Once metabolized, hormones are excreted for example-through the kidneys or bile-. Faster excretion processes reduce the time hormones remain active in the blood.

4.Efficiency of Negative Feedback Mechanisms: These mechanisms regulate hormone levels by decreasing hormone production when levels are sufficiently high, helping to maintain balance and prevent prolonged high levels.

The next few slides will explain this feedback inhibition process and its clinical implications in regards to hormonal insufficiencies



- **It is crucial not to abruptly stop glucocorticoid therapy especially after chronic use, as this can lead to withdrawal symptoms and adrenal insufficiency**

All in this box are Dr speech but with rephrasing for ur better understanding ✨

Understanding negative feedback is crucial for strategizing the management of endocrine disorders. For instance, cortisol deficiency can be from issues in the hypothalamus or the anterior pituitary gland or adrenal. If a person exhibits symptoms of cortisol insufficiency, it's **not** advisable to administer cortisol without further diagnostic testing. It's essential to perform tests to determine whether the deficiency originates from the pituitary gland, the adrenal glands, or the hypothalamus. 😱 But the Question here is how? by these two steps:

1. Administer CRH: If cortisol levels are low, administer (CRH).

Then, Observe Cortisol Response:

***If cortisol levels increase after CRH administration**: The adrenal glands are responsive, indicating the issue may lie within the hypothalamus (insufficient CRH production). So we give the patient CRH as therapy.

***If cortisol levels do not increase:** This suggests a problem in the pituitary or adrenal glands.

🔴 As we excluded hypothalamus dysfunction by the previous test , our candidates now are Pituitary dysfunction **VS** Adrenal dysfunction 😎🚩

2. ACTH Stimulation Test: Administer synthetic ACTH and measure cortisol response:

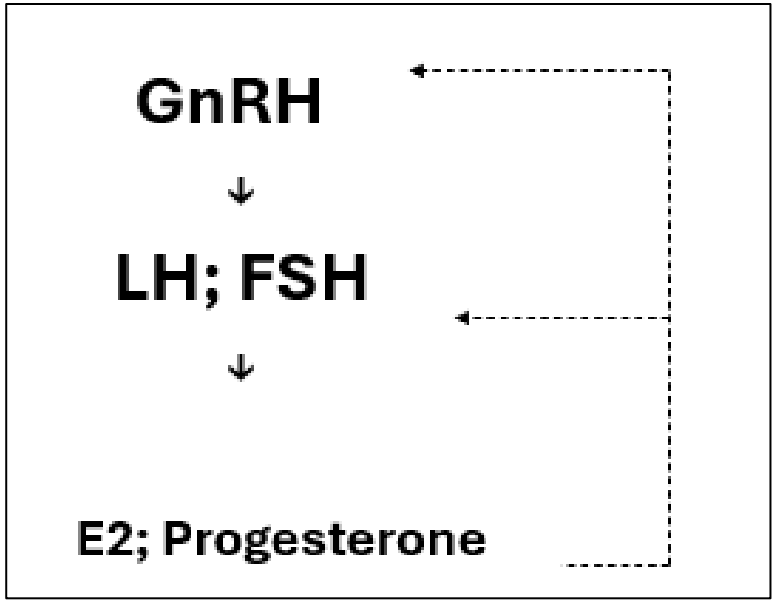
***If cortisol levels rise after ACTH administration:** The adrenal glands are functioning correctly, and the problem is likely in the pituitary gland (secondary adrenal insufficiency).

***If cortisol levels do not rise:** This indicates adrenal insufficiency, meaning the adrenal glands themselves are not functioning properly (primary adrenal insufficiency) and here u should give cortisol

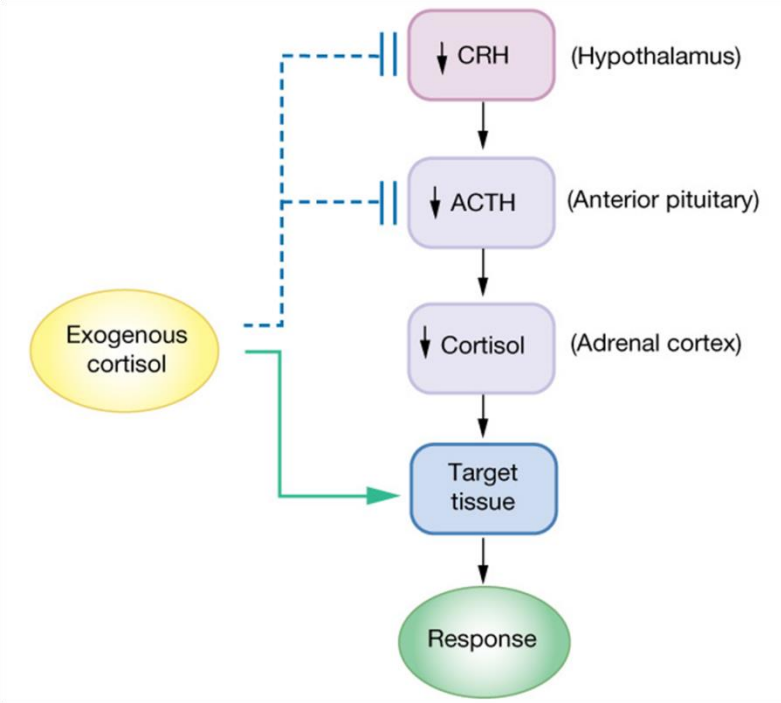
This is Dr speech, but with rephrasing

1. ⛔ **Risks of Oral Contraceptives**: Taking oral contraceptives can be risky, as there is a 5 - 10% chance of irreversible effects. This axis shown in pic, need to return back to normal after Oral Contraceptives, can take months to years and may not fully revert to its original state!

2. 🔴 **Hormone Therapy for Postmenopausal Women**: Estrogen and progesterone are administered to postmenopausal women. These hormones are then excreted in the urine through active secretion. By analyzing extracted hormones from the urine, we can manage and monitor treatment effectively.



The blue line is negative feedback



- **Sources of hormones:**

- Natural

Human (LH & FSH; hCG); Animal (T_3 & T_4)

Thyroid hormones can be taken from pigs, cows, because it has the same structure as human's hormone

- Synthetic

Most hormones and their antagonists

- **Disorders affecting endocrine glands:**

- Deficiency states

. HRT

. Drugs that induce synthesis and/or release, or drugs that induce affinity or sensitivity or number of receptors to hormone

- Excess production of a specific hormone

Inhibitors to the synthetic machinery or
Release inhibitors or
Specific antagonists or
Surgery; removal of the gland

- **Clinical pharmacology of hormones:**

- Major clinical use of hormones

HRT: Hormone replacement therapy (physiological doses)

- Supra-physiological doses (pharmacological doses) such as:

Anti-inflammatory effects (non-endocrine-related diseases)

- Use as diagnostic tool (TRH test ...)

Additional to understand prev. slide !!

-Hormone Replacement Therapy (HRT):

Used to replace hormones that are at low levels due to disease, aging, or other conditions.
Example: Estrogen and progesterone in post-menopausal women to alleviate symptoms of menopause like hot flashes and to reduce the risk of osteoporosis.

-Supra-physiological Doses (Pharmacological Doses):

Higher than normal doses of hormones are used to achieve effects other than simple replacement.
Example: Inhaled corticosteroids are commonly prescribed to control chronic asthma by preventing and treating the inflammation that constricts the airways.

-Use as Diagnostic Tools:

Hormones or hormone-releasing factors are administered to test the function of specific endocrine pathways.
Example: The TRH test –which we'll talk about later - involves administering TRH to stimulate the pituitary to release TSH. This helps in diagnosing disorders of the thyroid gland.

- **The use of some drugs which are not hormones, but used in the management of diseases of endocrine origin**

Antithyroid drugs, oral hypoglycemic agents…

- **Some drugs are used to treat diseases not related to the endocrine system but affecting it**

Anticancerous drugs → ♂ & ♀ infertility can affect ovum and sperms

- **The use of hormones as contraceptives??? As we said in slide 31**

1.Antithyroid Drugs: Used for hyperthyroidism, these drugs inhibit thyroid hormone synthesis, reducing excessive hormone levels and alleviating symptoms like rapid heartbeat.

2.Oral Hypoglycemic Agents: -pay attention their name is Hypoglycemic , so they work to decrease glucose- Used for type 2 diabetes, they reduce blood sugar by enhancing insulin sensitivity..

Impact on Endocrine Function:

•Anticancerous Drugs: Chemotherapy agents, can cause infertility by damaging the DNA in reproductive cells, leading to decreased reproductive function in both men and women

و أعلم أن النصر مع الصبر، و أن الفرج مع الكرب، و أن مع العسر يسرا

GOOD LUCK