ENDOCRINE
PHARMACOLOGY

01

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BASIC PRINCIPLES

- **Endocrine pharmacology vs endocrine physiology**

Not much of a difference between them, the physiologist talks about hormones as they are normally secreted from the body & the pharmacologist talks about them as drugs.

- **2nd in importance to CNS**

The hypothalamus is part of the CNS so anything affecting the CNS may be reflected on the endocrine system.

➢ **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,** very quickly because they are **ductless glands.**

➢ **Hormonal regulation ↑↓**

- **Growth & development**
- **Reproduction, fertility, sexual function**
- **Response to environmental situations (stress…)**
- **Maintenance of normal homeostasis**

HORMONES

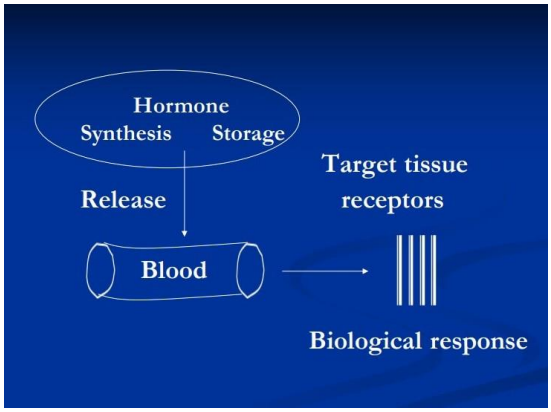
❖ **Chemical substances synthesized in and released from highly specialized cells collectively known as endocrine glands, immediately secreted into blood stream and act at some other place.**

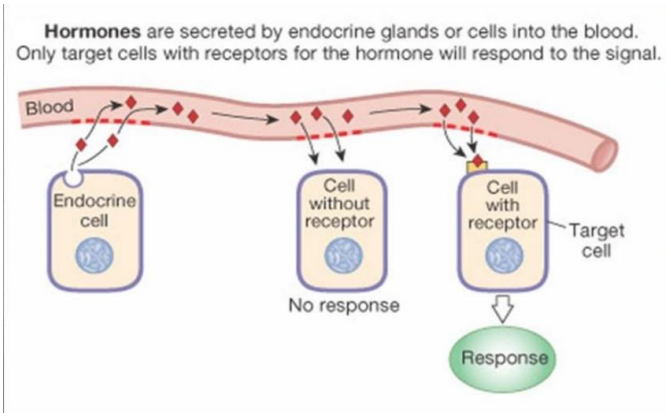
❖ **Considered cell to cell communication molecules.**

❖ **Transported by blood.**

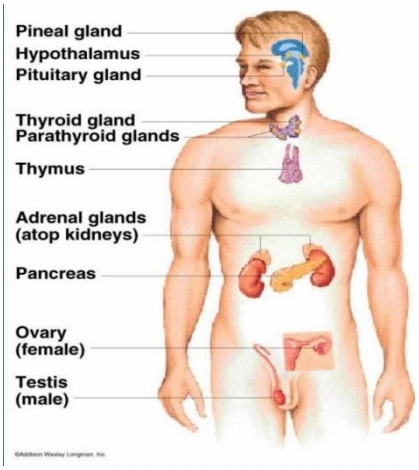
❖ **Distant or local target tissue receptors.**

❖ **Activates physiological response.**





- **Glands**
  - **Ductless, Hypothalamus** (of the CNS contains numerous nuclei and synthesize the posterior pituitary hormones), **Pituitary** (in sella turcica)**, Thyroid** (in the neck), **Parathyroid** (4 in the posterior of the thyroid)**, Pancreas** (in the abdomen posterior to the stomach in the upper abdomen) **, Adrenals** (above the kidney), **Ovaries** (in the pelvis**), Testes** (scrotum)



CHEMICAL NATURE OF HORMONES

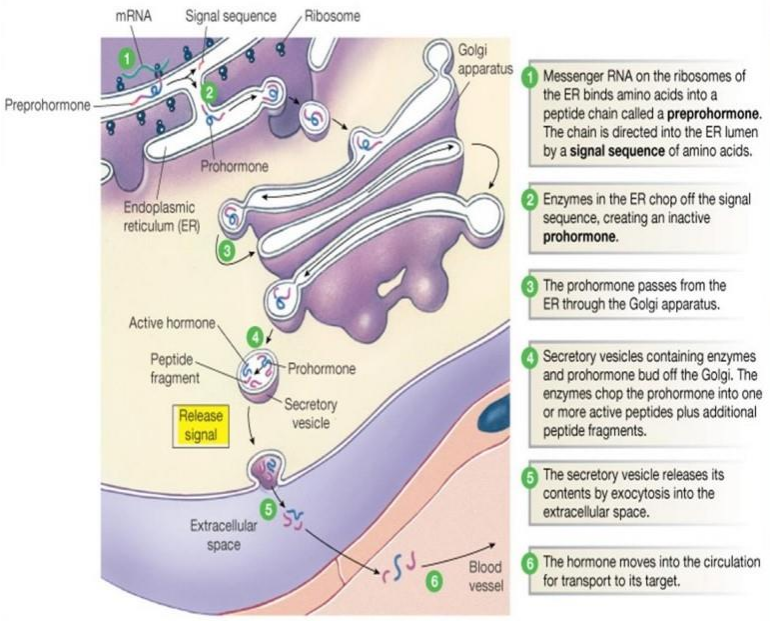
- **amino acid derivative: T3; T4; Dopamine (precursor=Tyrosine)**
- **Small peptides; polypeptides; large proteins or glycoproteins: Hypothalamic hormones; GH; PRL; Insulin; Glucagon; LH; FSH; TSH…**
- **Steroids: Cortisol; Aldosterone; Estrogen; Progesterone; Androgens**

AMINE HORMONES

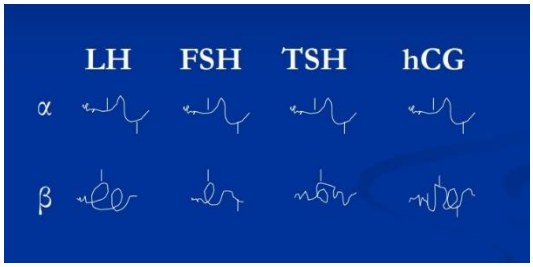
- **Derived from the amino acid tyrosine.**
- **Include the catecholamine dopamine & thyroid hormones.**
- **Stored until secreted.**
  - **Receptor locations Surface (Dopamine) Intracellular (nuclear; T3 & T4).**

PROTEIN AND POLYPEPTIDE HORMONES: SYNTHESIS AND RELEASE

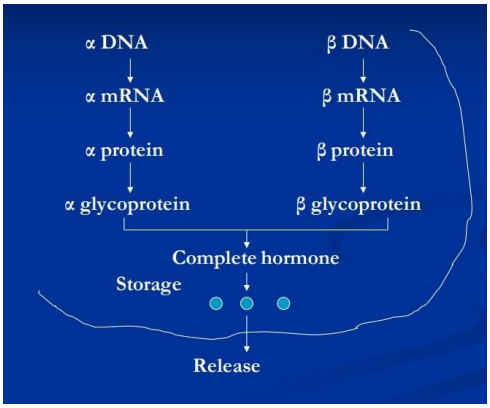
- important notes about the picture: (other than the mechanism).
  - protein hormones originate from specific genes, and they originate from larger precursors that can be used clinically to treat certain endocrine disorders.
  - We also have available synthetic recombinant.



- The difference between alpha & beta subunits in glycoproteins.
  - The alpha subunit is encoded by a single gene, And almost similar in this type of protiens.
  - The beta subunit is encoded by different genes, and differs between proteins, it is believed the activity of hormone is mainly by the beta subunit.
    - It can be proven by binding for example the alpha subunit of LH with the Beta subunit of TSH the activity is going to be that of TSH.

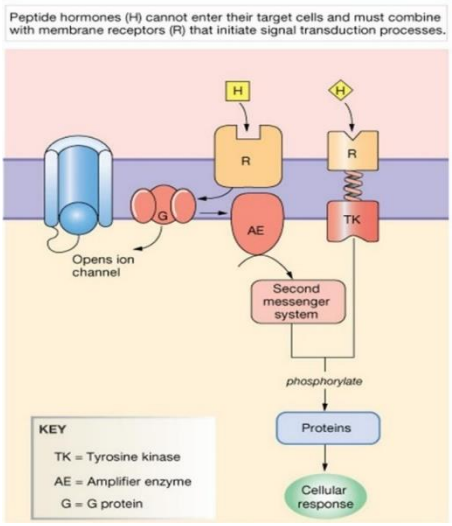


- Again, here are the steps for synthesizing hormones of protein nature, we must understand these steps because they can become potential drug targets, as in excess production of such hormones.
- drugs that target hormone synthesis are characterized by having a delayed onset because the synthesis usually takes time, in contrast to the drugs that act on the release.

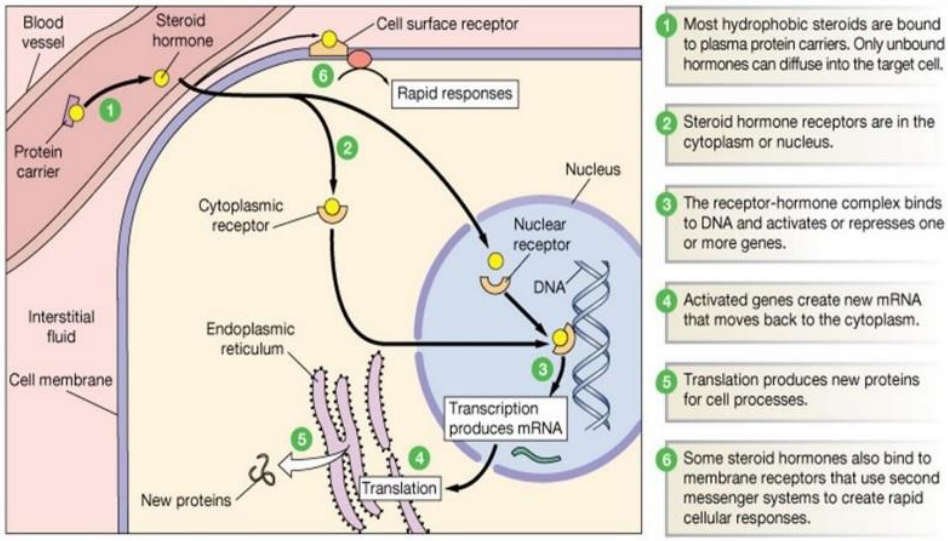


PROTEIN AND POLYPEPTIDE HORMONE RECEPTORS

- Bind to <u>surface receptor.</u>
- Transduction:
  - System activation
  - Open ion channel
    - Enzyme activation
    - Second messenger systems
    - Protein synthesis



STEROID HORMONES RECEPTORS

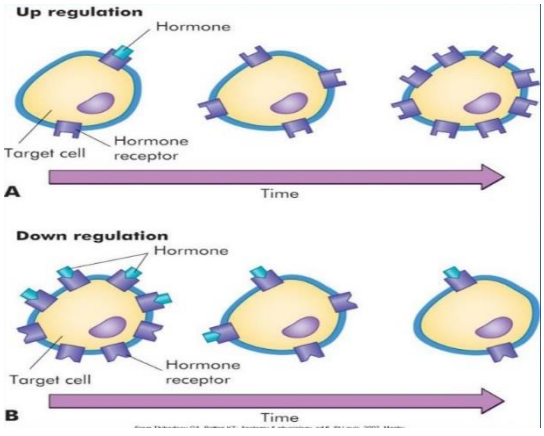


Please pond the figure to see the mechanism, notice some steroid hormones have cell surface receptors.

Hormone receptors are subject to 2 important phenomena:

Upregulation: increase in the number of receptors. (ex: oral hypoglycemic agents that are used in T2DB, they act by increasing sensitivity (number) to insulin receptors in peripheral receptors)

Downregulation(desensitization): decrease in number of receptors. (Ex: downregulation of insulin to its own receptors)

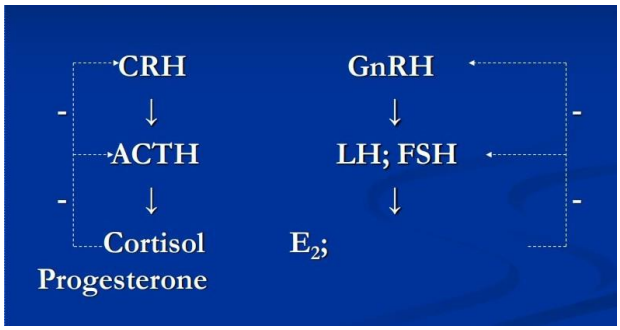


- **Basal conditions→minimal release,** whenever they're needed they are excreted or synthesized in tremendous amount.
- **Stimuli:**
  - **Nerve impulse**
  - **Change in composition of ECF,** e.g., hyperglycemia(insulin), hypoglycemia (glucagon), hypocalcemia (PTH).
  - **Another hormone (trophic hormone) blood → target cells → receptors → initial change → cascade of reactions → recognizable change.**
    - Trophic hormone: Hormone that can stimulate another hormone.
  - **Change in cell permeability. (**Insulin to glucose**)**
  - **Stimulation or inhibition of protein synthesis (Transcription or translation)**
  - **Stimulation or inhibition of mediator release (second messenger) (cAMP; DAG; Ca++; ITP (IP3) ...)**

You can know the type of 2nd messenger by adding it to certain cells that respond to a certain hormone, if there is a response then this hormone uses this type of 2nd messenger.

- **How long does a hormone stay high in blood?**

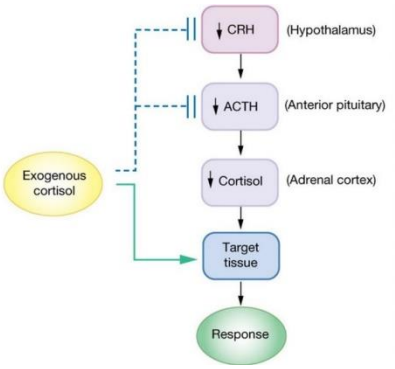
  Depends on:
  - **Extent of protein binding.**
  - **Efficiency of degradable enzymes & clearance (Metabolism & excretion).**
  - **Efficiency of negative feedback mechanisms.** (As in hypothalamic - pituitary - adrenal gland axis) →



- Understanding the basis of negative feedback helps put the strategy in the management of such diseases.
- And to help give the proper treatment.

(Ex: elevated ACTH & CRH & there is a cortisol deficiency, it can be primary or secondary or tertiary, it could be due to a problem in hypothalamus or pituitary or adrenal gland, so it's important to know the reason to give the proper treatment either administration of cortisol or ACTH etc...)

Another important reason is in the management of conditions when treating with exogenous hormones:



examples:

1. when treating with corticosteroid as an anti-inflammatory agent, their pituitary-adrenal axis is normal, so when giving exogenous cortisol its gonna suppress endogenous corticosteroids, when you decide to stop the exogenous cortisol, you must be careful and withdraw slowly or it may lead to sudden death.
2. Oral contraceptive pills (combination of estrogen & progesterone) Work on pituitary–gonadal axis and suppress release GNRH, LH, FSH by ovaries. but it turns back to normal in 90% of females after at least 6 moths, and some cases it may lead to atrophy of cells & infertility.

SOURCES OF HORMONES:

- **Natural: Human** (**LH & FSH** to treat infertility, taken from urine of postmenopausal ladies**, hCG** hormone of pregnancy extracted from urine of pregnant ladies, used to treat infertility & in in vitro fertilization**); Animal (T3 & T4)** from glands of animals
- **Synthetic Most hormones and their antagonists (**associated with less allergic reactions compared to natural, made through recombinant DNA technology)

DISORDERS AFFECTING ENDOCRINE GLANDS:

- **Deficiency states.**
  - **HRT.** Hormone replacement therapy → major clinical use of most hormones.
  - **Drugs ↑ synthesis and/or release, or drugs ↑ 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** of gland.

CLINICAL PHARMACOLOGY OF HORMONES:

- **Major clinical use of hormones HRT (physiological doses –** small doses**)**
- **Supra-physiological doses (pharmacological doses→** larger doses**)**

  Anti-inflammatory effects (non-endocrine-related diseases→ larger doses**) ...**
- **Use as diagnostic tool (TRH test ...)**
- **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.
- **The use of hormones as contraceptives.** (as in the pills we talked about above)