Endocrine system 2

Pharmacology

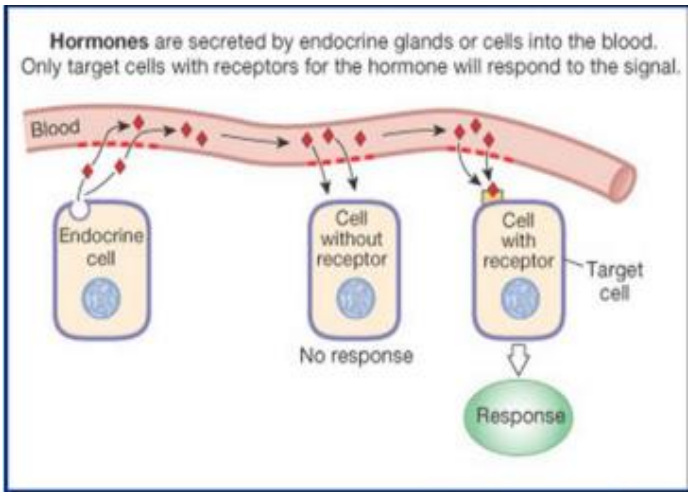
Writer: Ahmad T Qatawneh
Corrector: Hanna Arikat
Doctor: Suheil Zmeli

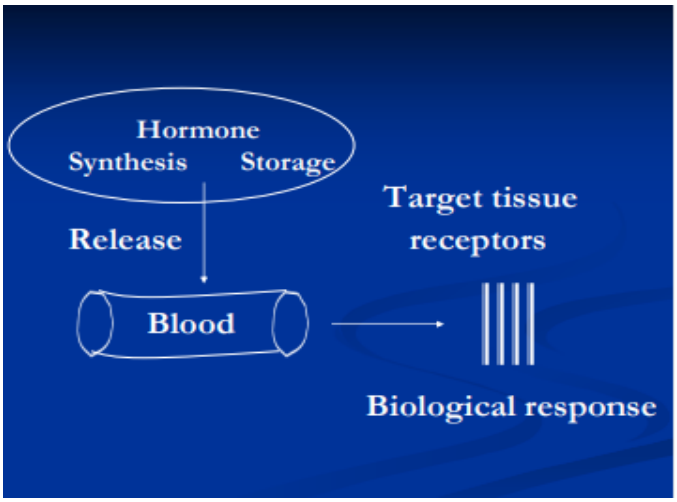
• Basic principles about Endocrine Pharmacology:

- Terms-wise, **Endocrine pharmacology** focuses on the use of hormones and preparation for treating of disorders whereas **Endocrine physiology** focuses on the normal secretion of hormones and their actions inside the body (Both are often used interchangeably).
- The endocrine system comes as second in importance following the CNS keeping in mind that Both systems are closely correlated to each other, Example: The Hypothalamus is considered a part of the CNS, yet regulates certain aspects of the endocrine system.
- **General Features of the endocrine system**:
  1- Uses chemical signals (Hormones) for cell-cell communication.
  2- Coordinates the functions of cells.
  3- Response to an endocrine signal occurs within minutes to hours(Due to being ductless).
- **Endocrine glands are subjected to hormonal regulation** involving both stimulation or inhibition, Examples:
  1- **Secretion of Prolactin** is under negative control of Dopamine.
  2- **Growth and development** (GH from Thyroid gland).
  3- **Reproduction, fertility, and sexual drive and gratification**.
  4- **Response to environmental situations** (Stress leading to Cortisol secretion).
  5- **Maintenance of homeostasis** (Blood sugar levels regulated by Insulin/glucagon as well as certain hormones regulating fluid and electrolytes balance).

• Hormones: More in depth

- 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 towards Distant or local target tissue receptors thereby Activating physiological response as demonstrated by the following figures:





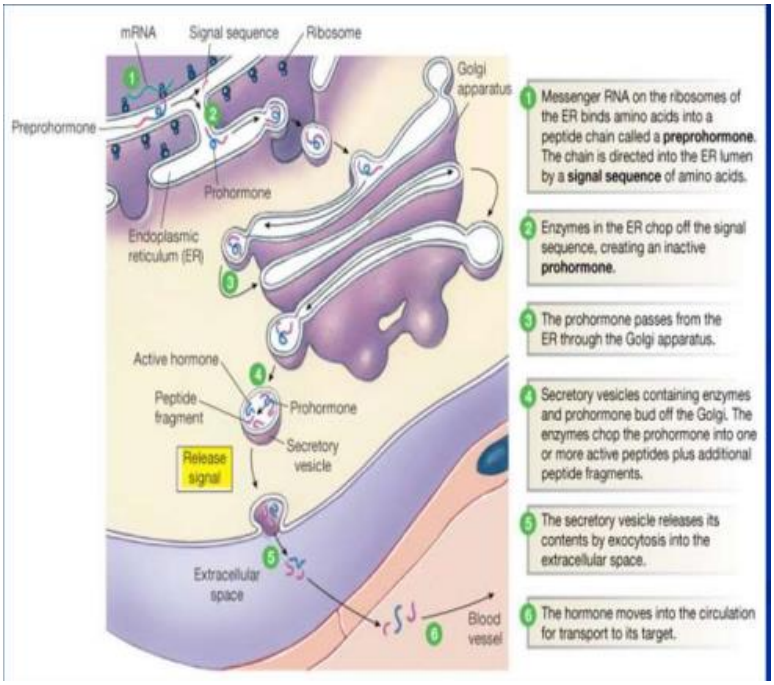
- There are numerous **Endocrine (Ductless) glands** throughout our body secreting hormones:
  1- **Hypothalamus** (Part of CNS)
  2- **Pituitary gland** (Base of the skull)
  3- **Thyroid gland** (In the neck)
  4- **Parathyroid gland** (Posterior surface of the thyroid).
  5- **Pancreas** (Mixed gland)
  6- **Adrenal (Suprarenal) gland**
  7- **Ovaries, Testicles (Gonads)**
- The chemical nature of hormones varies as such:

Amino acid (A.A) derivatives: (Derived from precursor=Tyrosine)
Thyroid hormones (Triiodothyronine (T3) and tetraiodothyronineThyroxine (T4))
Dopamine, a catecholamine released as a Neurotransmitter in the CNS and as a hormone in the Endocrine system.

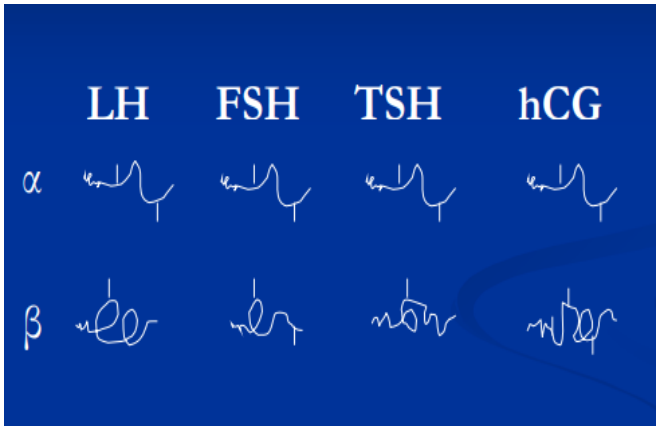
Small peptides; polypeptides; large proteins or glycoproteins: (Majority of hormones)
Hypothalamic hormones; GH; PRL; Insulin; Glucagon; LH; FSH; TSH and others.

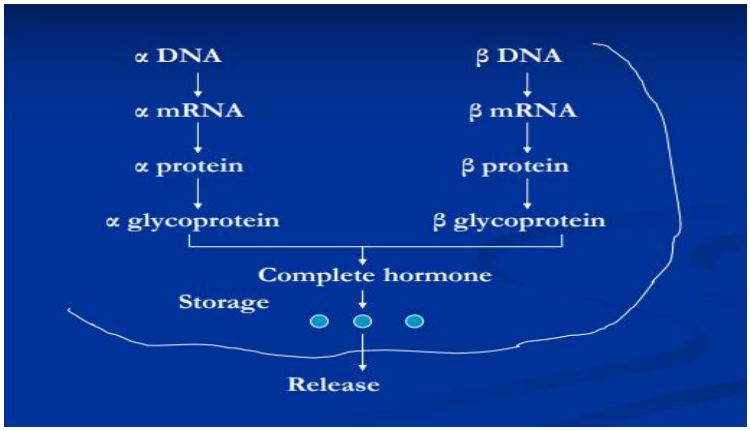
Steroids: (Derived from the Cholesterol (Sterol) Nucleus)
Cortisol, Aldosterone secreted from the Adrenal gland.
Estrogen, Progesterone and Androgens secreted from the gonads.

- **Amine Hormones**:
  Derived from the amino acid tyrosine, they include the **catecholamine dopamine** & thyroid hormones. These hormones are synthesized and stored until secreted by a stimulus. Their receptor's locations are Surface Receptors for (Dopamine) while Intracellular (nuclear; T3 & T4).
- **Protein and Polypeptide Hormones:**
  From the start, DNA is transcribed into mRNA then translated into immediately active hormones or sometimes precursors known as **Preprohormones (PreproInsulin)**. These precursors are directed towards the ER via an A.A signaling sequence which is then cleaved producing a Prohormone which will be directed towards the Golgi for the final modification by further cleaving it into the active hormone to be finally stored in granules and released when needed.



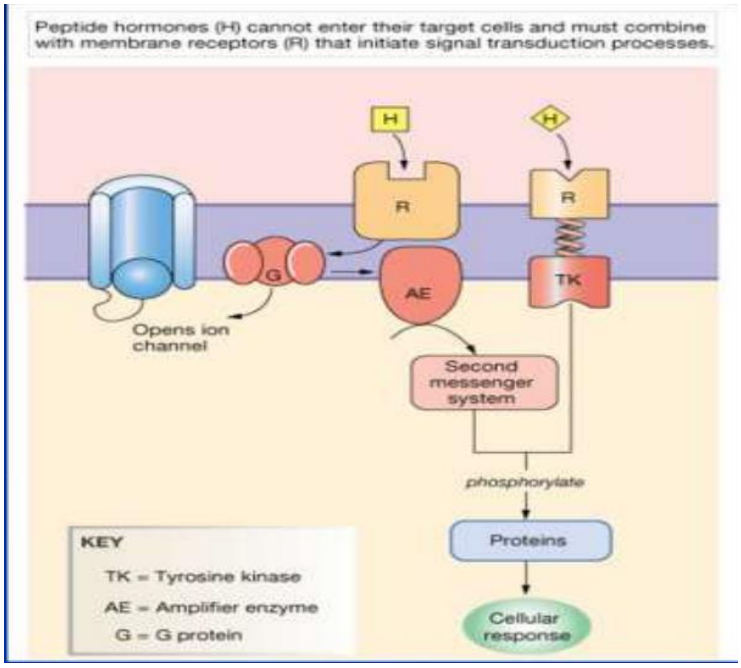
Clinically, Some Preprohormones have been synthesized using Recombinant-DNA tech to treat certain disorders (Example: Preproinsulin).





- ✓ **The figure to the left** shows examples of Protein hormones, each composed to an alpha and a beta subunit. While **the alpha subunit is encoded by same gene for all, the beta subunit is unique and therefore encoded by a different gene for each different hormone**.
- ✓ This fact can be demonstrated by inducing the dissociation of the subunits and then combining the alpha subunit of LH for instance and the beta subunit of TSH and upon examining the effect of this recombinant, the result is TSH-activity indicating that the beta subunit is different while the alpha is identical. **However**, certain finding suggest that the originals alpha and beta subunit of the hormone yield the maximal activity possible.
- ✓ **The figure to the right** shows the Cascade of events from DNA towards the release of the hormone. Any step along this pathway can be targeted by drugs. **Drugs targeting the synthesis process of these proteins are of slow-onset of action while those targeting the release process are of rapid-onset.**

- ✓ Protein hormones can't penetrate the cell membrane and therefore bind **cell surface receptors**, thereby inducing a conformational change leading to **signal transduction**:
  - **System activation** (Tyrosine kinase pathway activation by insulin).
  -**Open ion channel** via either Enzyme activation, Second messenger systems or Protein synthesis



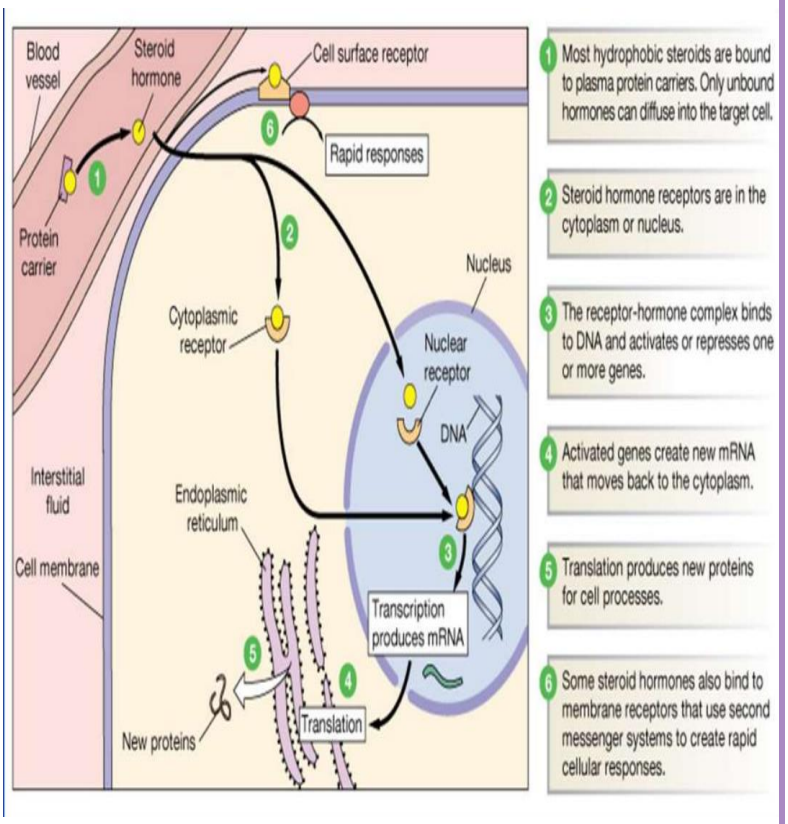
- **Steroid Hormones and their Receptors**:

Synthesized by glands and then secreted to travel throughout the blood in the bound form (bound to carrier proteins), only the unbound hormones can then affect their target cells via 3 routes:

1- Pass through the membrane to bind **cytoplasmic receptors** forming complexes that then go towards to nucleus to regulate DNA-expression.
2- Pass through the membrane to immediately bind **nuclear receptors**
3- Some of these hormones bind **cell surface receptors** to elicit a rapid cellular response.

Route 1,2 usually require time because the process of protein synthesis while Route 3 elicits a faster response.

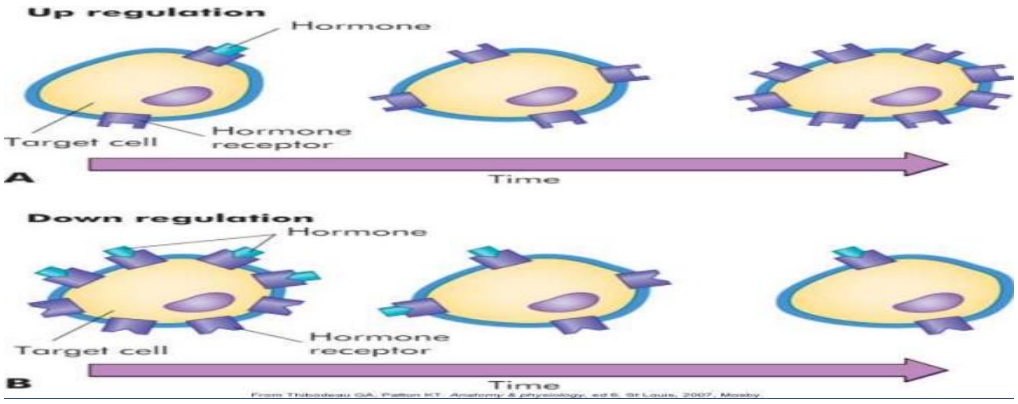
Note: Steroid hormones are hydrophobic substances and therefore cannot freely in the hydrophilic environment of the blood and thus need carrier proteins.



• The Concept of Sensitization and de-sensitization

➢ Hormones are subjected to 2 phenomena:

1- **Desensitization (Down-regulation)** : decrease in the number and/or affinity of receptors. It is considered the underlying mechanism behind DM where the patients are irresponsive to insulin despite being in high levels in the blood.
2- **Sensitization (Up-regulation)**: increase in the number and/or the affinity of the receptors for that hormone. Clinically, Oral hypoglycemic agents are used to induce the up regulation of Insulin receptors for the treatment of DM type 2.



- **Basal conditions** are defined as body conditions whereby we have minimal release of hormones. Upon Stimulation via **Nerve impulse, change in composition of ECF, or another hormone (Trophic hormone)**. are then released into the blood.

Examples:

1- During pregnancy, there is an increase in stimulation resulting buildup of Estrogen and Progesterone
2- increased prolactin secretion at the end of pregnancy
3- the mid LH surge in the middle of the menstrual cycle.

- Hormones reach blood → target cells → receptors → initial change → cascade of reactions → recognizable changes including:

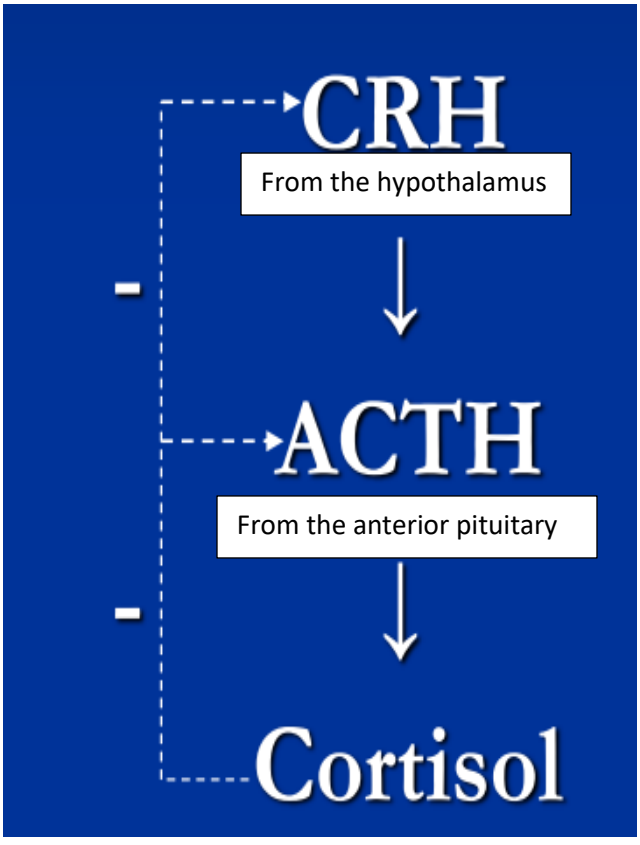
1- **Change in cell permeability**
2- **Stimulation or inhibition of protein synthesis** (Regulation of Transcription or translation)
3- **Stimulation or inhibition of mediator release (second messenger)** which can be proven by using laboratory methods, Examples on 2ndry messengers: cAMP; DAG; Ca++; ITP (IP3)...

- The time the hormone spends in high amount inside blood depends on:

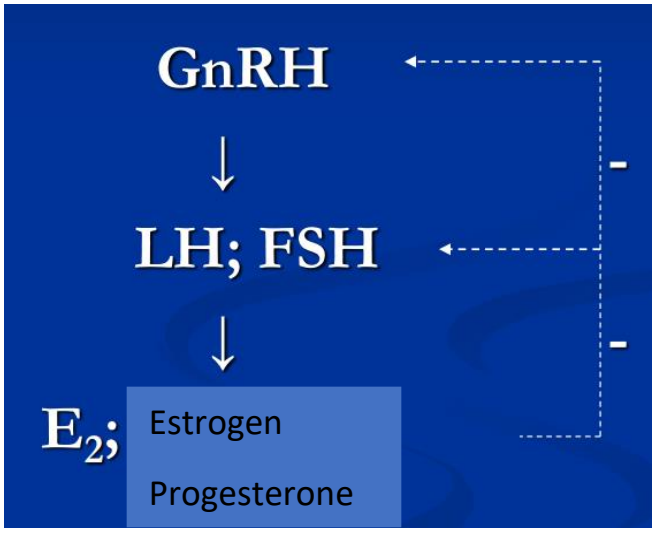
1- Extent of protein binding.
2- Efficiency of degradable enzymes & clearance Metabolism & excretion.''
3- Efficiency of negative feedback mechanisms.

• The concept of negative feedback mechanism:

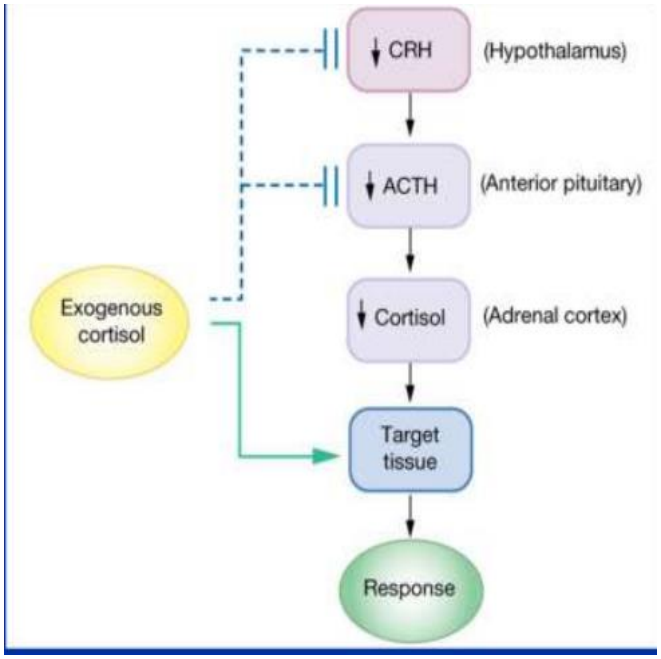
- This figure represents the **Hypothalamic-pituitary-adrenal axis** which is controlled by negative feedback mechanisms, Cortisol back feeding into ant-pituitary or the hypothalamus inhibiting ACTH, CRH release.
- Clinically, when dealing with Cortisol deficiency, we can identify the origin of the deficiency using Hormone assays (expensive). Thus, it better to **treat with replacement therapy regardless of the origin of the deficiency**.
- (**1ry** intrinsic to adrenal gland, **2ry** in the pituitary or **3ry** in the hypothalamus).



- In females, this is the hypothalamic pituitary gonadal axis, Same as the previous example regarding negative feedback loops.
- **In postmenopausal women**, there is a **decrease in estrogen and progesterone** and consequently, there will be an **increase in LH, FSH** which can be detected in urine test.
- **Clinical correlate**: Oral contraceptives usually contain estrogen and progesterone in certain amounts that can lead to suppression of the axis. In 90% of cases this suppression is reversible. In 10% of cases, the reversal takes from 6 month to even a case of irreversible suppression leading to infertility. ***Therefore, Newlywed ladies are advised not to use such agents*** before their first pregnancy in order to diagnostically tell whether their infertility is an intrinsic disorder or whether its extrinsic due to taking these oral contraceptives.



- This figure illustrates the effect of exogenous administration of cortisol on the adrenal axis. Upon chronic administration, there will be suppression of all **CRH**, **ACTH**, **endogenous cortisol** synthesis and secretion.
- This is why patients taking Cortisol for long periods of time are advised not to abruptly stop using the drug to avoid Adrenal suppression (decrease in the endogenous synthesis of cortisol).



- ## Sources of hormones:

- **Natural**

1- **From humans: GH** was previously extracted via a nasal procedure but not anymore due to bad SE. Also, **LH and FSH** are taken from the Urine of postmenopausal women. Finally **HCG**, known as the hormone of pregnancy, is produced by the placenta and therefore is found in high amount in Urine of pregnant women.

2- From Animals: Animal Insulin and from pigs and cows and theoretically humans but low bioavailability, thus replaced by synthetic Recombinant insulin and T3,T4.

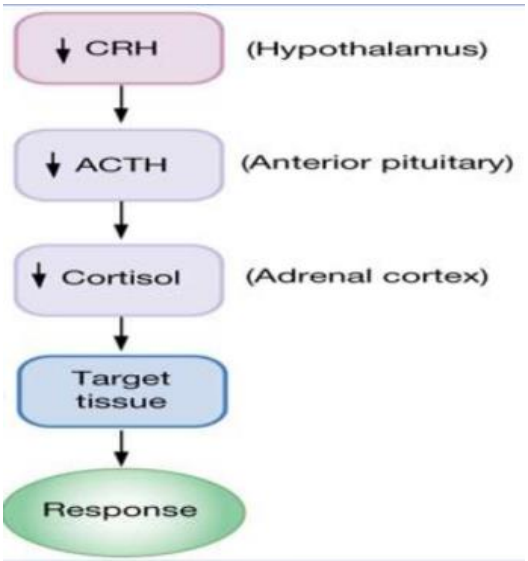
➢ **Synthetic**: Most supplied hormones and Their antagonists, synthesized by many techniques including Recombinant DNA.

• Clinical uses of hormones:

1- **Clinical disorders affecting the endocrine system**:

A- **Deficiency states**, for instance cortisol deficiency, treated by HRT (Hormone replacement therapy) by using Physiological dosages (10^-13-10^-9) for treating endocrine disorders

B- **Excess production of a specific hormone** by using Inhibitors to the synthetic machinery or Release inhibitors or Specific antagonists or Surgery.



2- **Anti-inflammatory effects (non-endocrine related diseases) by using supraphysiological dosages.**

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

Final notes:

- we can use some drugs which are not hormones but used in the management of diseases of endocrine origin, Examples: **Antithyroid drugs**, **oral hypoglycemic agents.**
- Some drugs are used to treat diseases not related to the endocrine system but affecting it Example: Anticancerous drugs → leading to ♂ & ♀ infertility.
- The use of hormones as contraceptives is controversial as discussed before.

The End