Unit 11: part 1
Clinical Endocrinology

Outlines:

- Physiology of Endocrine System
- General functions of hormone
- Classification of hormone
- Mechanism of hormonal action
- Regulation of hormonal secretion
- Disorders of the endocrine system Overview
- Assessment of endocrine functions
- Pituitary Gland Disorders
- Thyroid Gland Disorders
- Adrenal Gland Disorders
- Gonadal Disorders

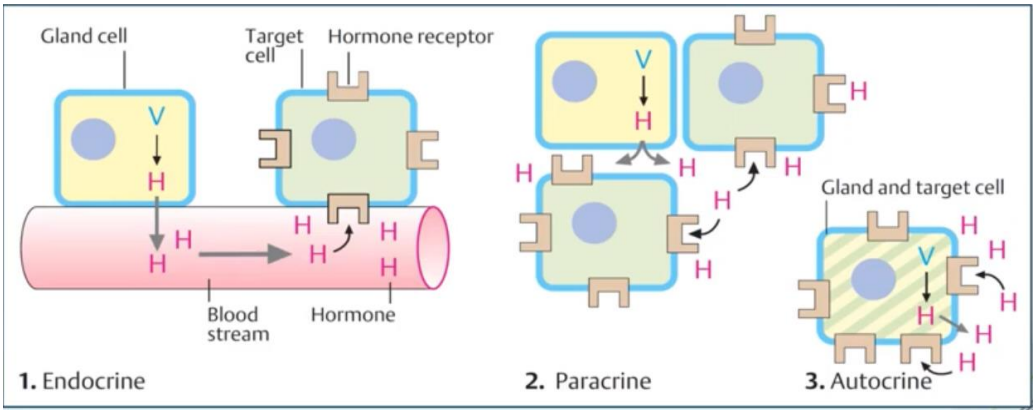
Introduction

Endocrine System:

- The endocrine system consists of group of glands and organs that regulate and control various body functions by producing and secreting hormones.
- The glands of the endocrine system **do not have ducts** but rather release their hormone directly into the bloodstream, so hormone are readily accessible to **laboratory evaluation.**
- **Hormones** are organic compounds secrete from the endocrine glands and circulate in the blood to act near to their site of release (local hormones) or at a distant organ.
- Hormones cause changes in physiologic and chemical processes that help to maintain body equilibrium or **homeostasis .**

Endocrine, paracrine, and autocrine hormone effects:

- **Endocrine hormones**: they migrate from their site of synthesis to the site of action in the blood (Insulin).
- **Paracrine hormones**: tissue hormones, the target cells for which are in the immediate vicinity of the glandular cells that produce them (GIT hormones).
- **Autocrine hormones:** they pass their effects back to the cells that synthesize them (Prostaglandins).



General functions of hormone

1. **Maintenance of internal homeostasis (state of dynamic equilibrium of the internal environment of the body that is maintained by processes of feedback and regulation in response to external or internal changes).**
2. **Regulation of metabolism: Hormone affect the metabolism of carbohydrates, proteins lipids and minerals, directing their synthesis, storage, mobilization and utilization according to body needs**
3. **Hormone support cell growth and development**
4. **Hormones have an important role in behavior such as fear, depression, and sex behavior biological clock.**
5. **Hormone coordinates reproduction.**
6. **Hormones facilitate responses to external stimuli**
7. **Hormones regulate some immune functions**

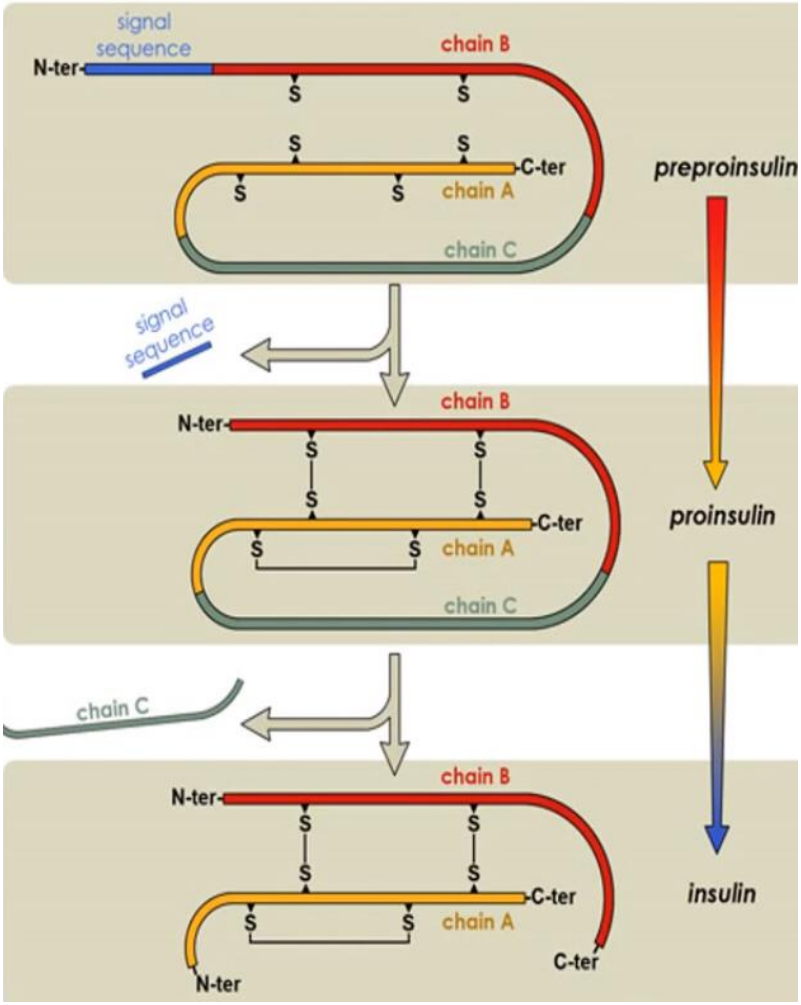
Classification of hormone

- **According to the chemical composition:**
  1. **Proteins: such as insulin, growth hormone, TSH, LH, FSH, parathyroid hormones, and prolactin**
  2. **Polypeptides: such as oxytocin, ADH and ACT**
  3. **Steroids: such as sex hormone (estrogen , progesterone, androgens) glucocorticoids (cortisol) mineralocorticoids (aldosterone)**
  4. **Amines or amino acid derivatives: such as thyroid hormone T3 & T4, epinephrine, norepinephrine and serotonin.**

- **According to the mechanism of action:**
  1. **Group I: Hormone that bind to intracellular receptors (lipophilic)**
  2. **Group Il: Hormones that bind to cell surface receptors then activate second messenger (hydrophilic)**

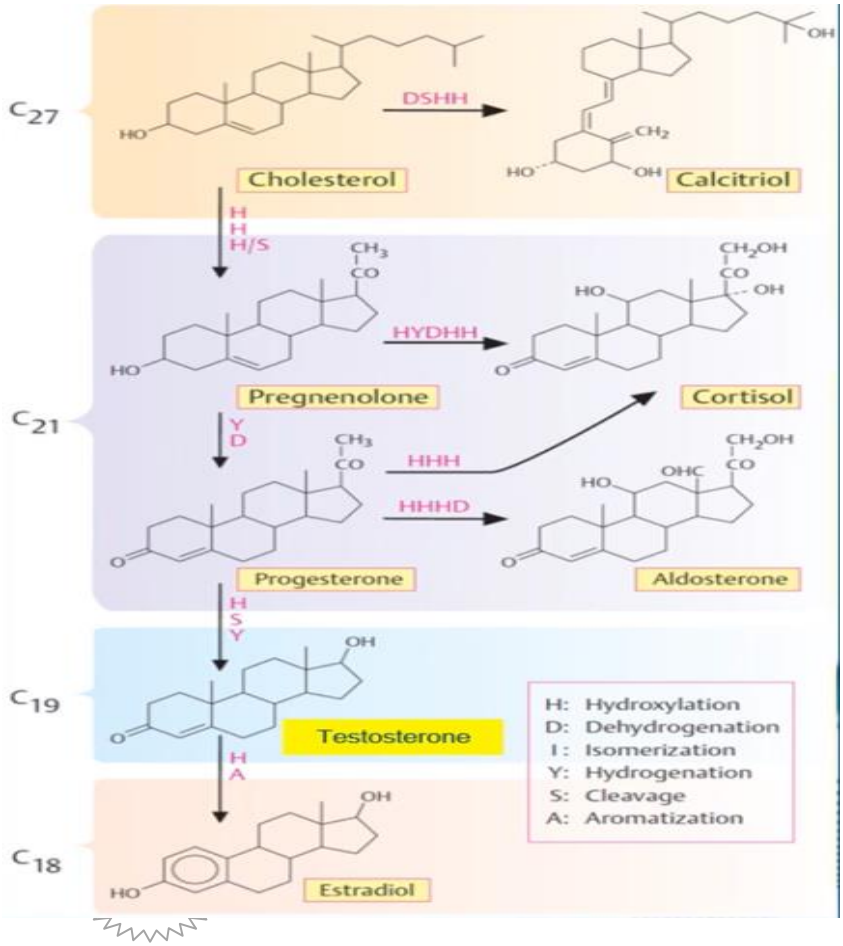
Protein hormone

- Protein hormone is synthesized in the endocrine glands as larger precursor called **preprohormone.**
- The leader sequence in preprohormone is cleaved after insertion in endoplasmic reticulum and gives **prohormone** molecule.
- Within the endoplasmic reticulum the prohormone is cleaved enzymatically and undergoes some modification to produce an **active hormone** molecule.
- Protein hormone **does not attach plasma protein and circulate free in the blood.**



Steroid hormone

- Steroid hormone is synthesized in the cytoplasm via multi-enzyme process.
- All the steroid hormone are derived from **cholesterol**
- They are derived into groups according to the C-number; C18 are **estrogens**, C19 are **androgens** and C21 are **glucocorticoids**, **mineralocorticoids** and **progestin.**
- Within the plasma the steroids **bind to specific plasma protein**, which allow them to circulate in blood stream for time **longer** than the free hormone.



Mechanism of hormonal action

➢ **Group I: Hormone that bind to intracellular receptors**

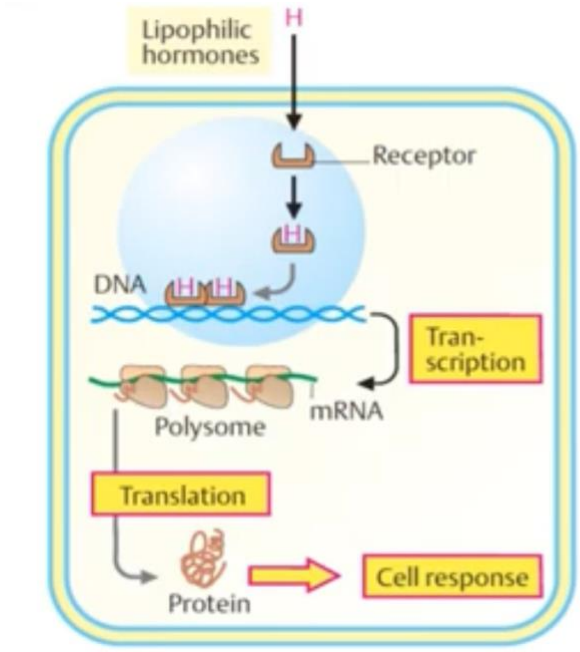
- **These hormone can pass easily through the cell membrane (lipophilic hormones) and bind to specific receptor protein in cytosol or nucleus, forming hormone-receptor complex.**
- **The hormone-receptor complex binds to a specific region of DNA called hormone response element (HRE) inducing formation of mRNA**
- **The mRNA enters the cytoplasm and initiate the synthesis of the protein or peptides that carry out the action caused by the hormone**
- **Androgens, Estrogens, Progestin's, Glucocorticoids, Mineralocorticoids, Calcitriol, Thyroid hormones (T3 and T4)**

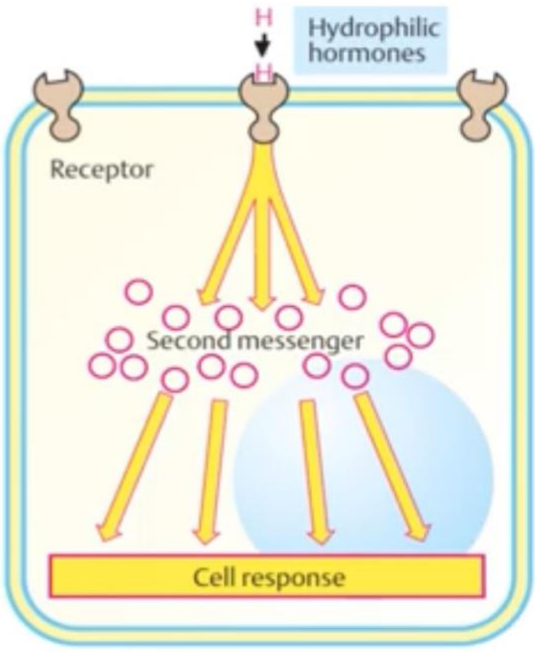
➢ **Group Il: Hormone that bind to cell surface receptors :**

- **A hormone, which is the first messenger; binds to specific receptor on the outer surface of the cell membrane as it cannot cross the cell membrane (hydrophilic hormones)**
- **The hormone receptor complex affects a second messenger that modifies metabolic intracellular process. *The second messengers are:***

1) **cAMP: ACTH, ADH, Calcitonin , CRH, FSH, LH, Glucagon, Insulin, PTH, TSH**
2) **CGMP: atrial naturetic factor and nitric oxide**
3) **Ca^{2+} /phosphatidylinositol: ADH, CCK, Gastrin, GRH, Oxytocin, TRH**
4) **Kinase or phosphatase: Erythropoietin, GH, Insulin, Prolactin**

Mechanism of hormonal action

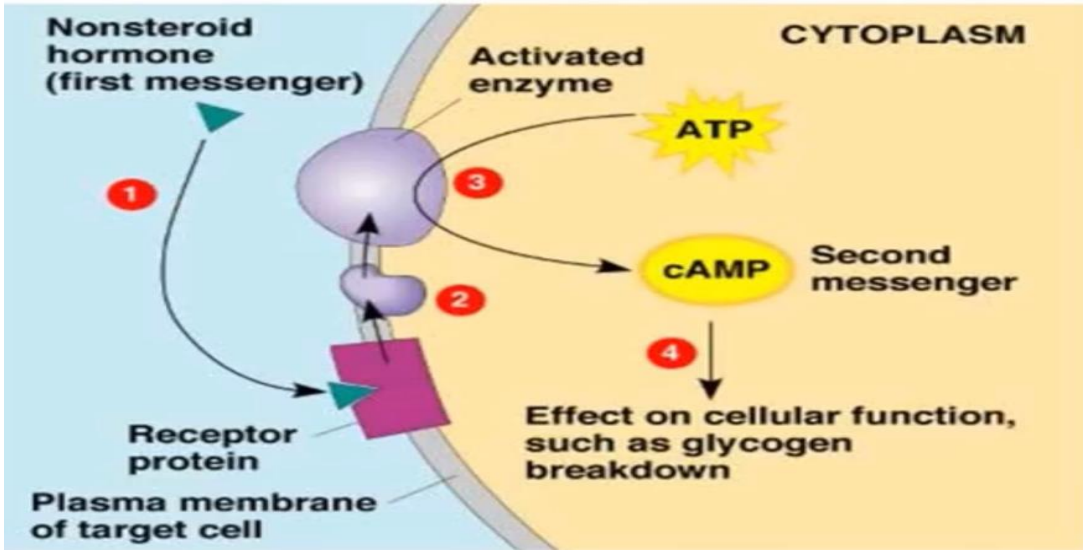




the different mechanism of Group I and Group II:

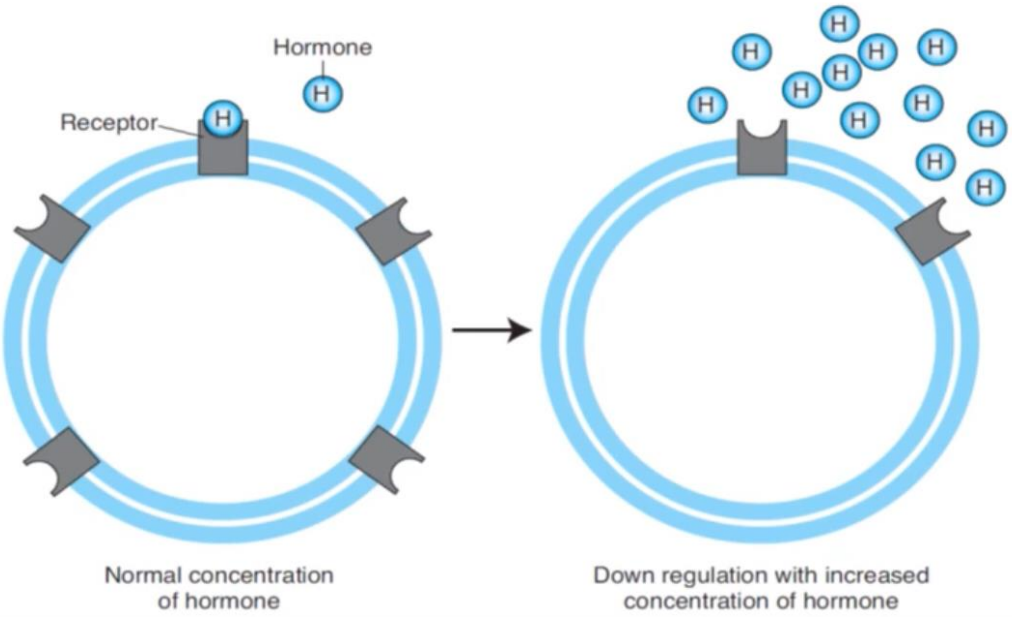
	Group I	Group II
Types	Steroids, iodothyronines, calcitriol	Polypeptides, proteins glycoproteins, catecholamines
Solubility	Lipophilic	Hydrophilic
Transport proteins	Need to be carried on protein in blood because they are H_2O insoluble	They are H_2O soluble and not bound to carrier protein for transportation in blood
Plasma half-life	Long (hours to days)	Short (minutes)
Receptor	Intracellular	Cellular membrane
Mediator	hormone receptor complex	cAMP, cGMP, Ca^{2+}/phosphatidylinositol and Kinase or phosphatase cascade

Signal transduction



Down-regulation of Receptors

- **Exposure of receptors to high concentrations of hormone may decrease the number and affinity of surface receptors (down-regulation or desensitization)**
- **This phenomenon is seen in obesity , where high levels of insulin occur, This results in a decreased sensitivity of cells to insulin leads to type-2 DM**



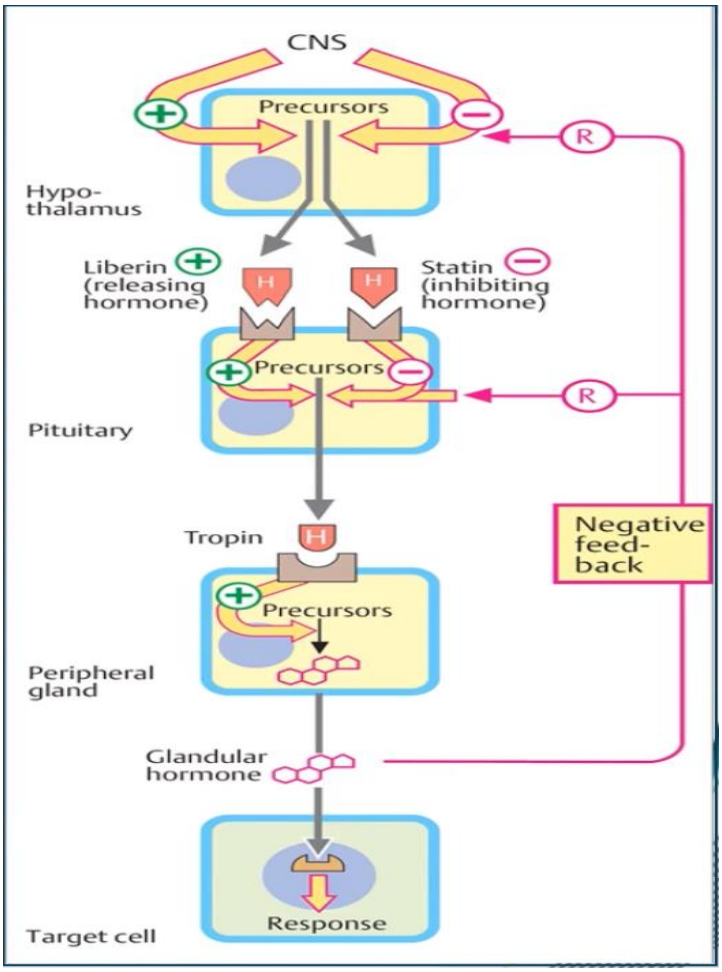
Regulation of hormonal secretion

1) **Stimulatory Or inhibitory signals such as hypothalamic factors, pituitary hormone and neurotransmitters**
2) **Circadian rhythm or diurnal variations: such as ACT has the peak level at 8am while GH has the peak level at night.**
3) **Many hormone are released in pulsatile fashion such as GHRH**
4) **Feed-back regulation**

- **The final secrete hormone regulates its own secretion through inhibition of the secretion of one Or more of the precursor hormones**
- **When a peripheral hormone level is increased above threshold Level, this will supers releasing of precursor hormones. When its level is decreased below threshold Level, this will stimulate releasing of precursor hormones (like the thermostat that regulates the heating/cooling cycles In refrigerator)**

Feed-back regulation of Hormone

- **Releasing hormones: they are secreted by hypothalamus and control the release of other hormone (tropic hormones) from the pituitary gland.**
- **Tropic hormones: they are secreted by pituitary gland (master gland) and they control the release other hormone (peripheral hormones) from endocrine glands.**
- **Peripheral hormones: they are secrete by peripheral endocrine glands and responsible for the tissue response and feedback regulation.**



Disorders of the endocrine system

- **There are two main categories of endocrine disorders "Primary and secondary "**
- **Primary disorders include problems with the gland itself which leads to either hyper-secretion or hypo-secretion (defects are in the peripheral gland)**
- **Secondary disorders where the glands are functioning normally, however the outside stimulating agents are either in excess resulting in hyper-secretion or deficient resulting in hypo-secretion (defects are in the pituitary gland or the hypothalamus)**
- **Hyper-secretion of hormone is more difficult to treat than hypo-secretion.**
- **Hyper-secretion is treated by gland inhibition or partial removal**

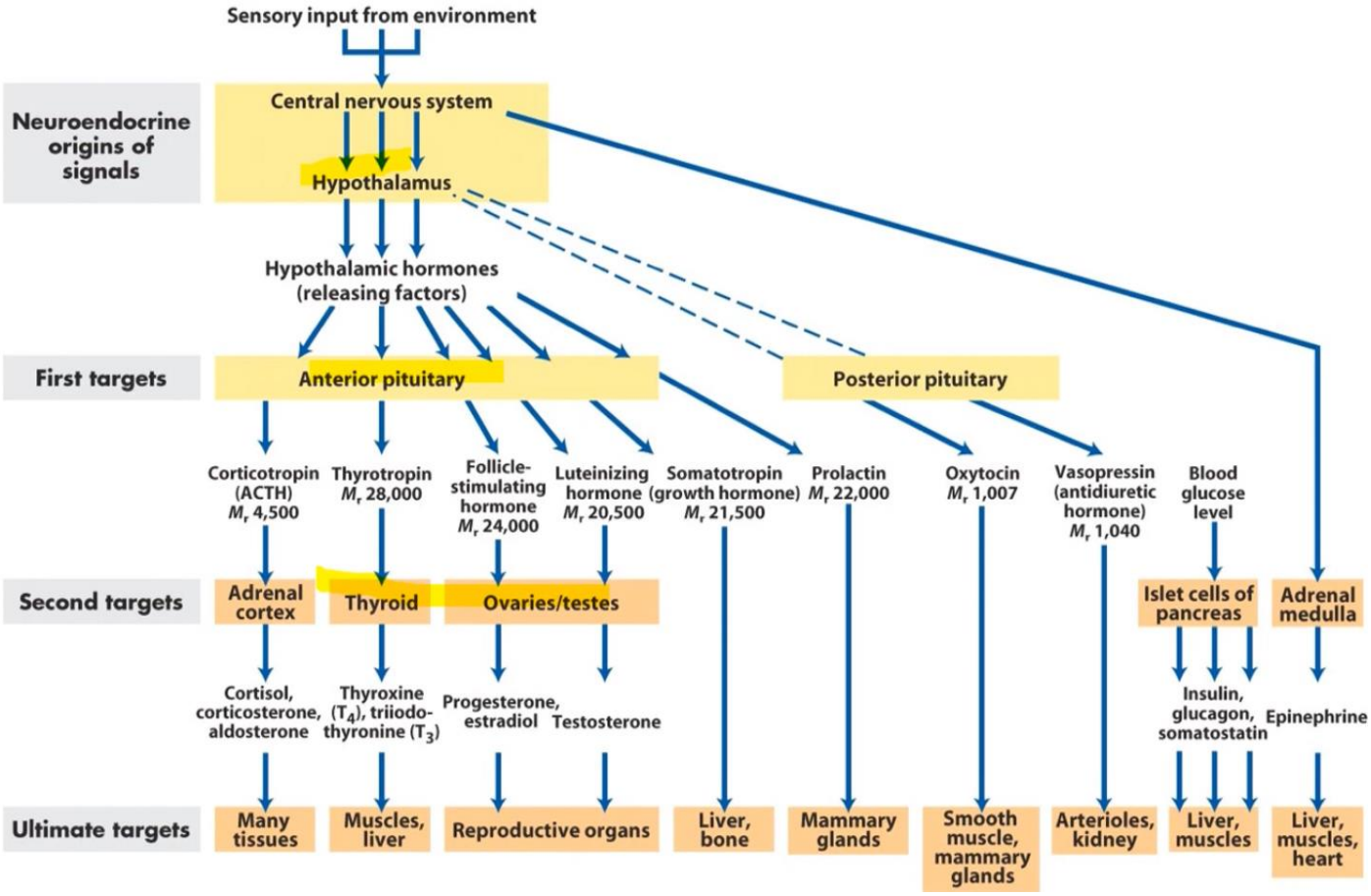
- **Whereas <u>hypo-secretion</u> is treated by <u>hormone replacement therapy</u>.**

Hypothalamic hormones

Hormone	Major function
Corticotrpoin releasing hormone (CRH)	↑ ACTH
Thyrotropin releasing hormone (TRH)	↑ TSH
Gonadotropin releasing hormone (GnRH)	↑ FSH and LH
Prolactin inhibiting factor (PIF)	↓ Prolactin
Prolactin releasing factor (PRF)	↑ Prolactin
Growth hormone releasing hormone (GHRH)	↑ GH
Growth hormone inhibiting hormone (somatostatin)	↓ GH
Antidiuretic hormone (ADH)	↑ Water reabsorption
Oxytocin	Vasoconstriction of smooth muscle Stimulate uterine muscle contraction

Pituitary gland hormones

Hormone		Major function
Anterior lobe	Growth hormone (GH)	Stimulates body growth
	Prolactin (PRL)	Stimulates breast tissue for milk synthesis
	Adrenocorticotrophic hormone (ACTH)	Stimulates adrenal cortex to release glucocorticoids
	Thyrotropin stimulating hormone (TSH)	Stimulates thyroid to release T3 and T4
	Luteinzing hormone (LH)	Stimulate ovaries in female and testis in male to produce sex hormones Maturation of both ovum and sperms
	Follicle stimulating hormone (FSH)	
Posterior	Posterior pituitary lobe only stores the Oxytocin and ADH	



Assessment of endocrine function

- **There are some difficulties in the endocrine assessment:**
  1. **Low concentration of hormone in blood, sometimes the hormone concentration is below the detection limit**
  2. **Variability due to circadian rhythm and pulsatile fashion of release**
  3. **Hormone binding to proteins: the unbound or free fraction of the hormone is the biologically active and responsible for feedback regulation.**
- **Pitfalls in interpretations.**
  1) **1Immunoassay interference: presence of unsuspected antibodies that can interfere with the hormone being measured.**
  2) **Log-linear response: dose response curve is usually not linear.**

Dynamic function tests (DFTs)

- **Where the results of clinical assessment and baseline biochemical investigation fail to rule in or rule out a serious endocrine diagnosis, dynamic function tests may be required.**
- **DFTs involve either stimulating or suppressing a particular hormonal axis and observing the appropriate hormonal response.**
- **If deficiency is suspected ⟶ stimulation test (by tropic hormone or physiological stress)**

- **If excess is suspected ⟶ suppression test**

1) *Insulin stress test :(insulin tolerance test)*

- **For hypopituitarism**
- **It measures the ability of anterior pituitary to produce GH and ACTH (cortisol is measured instead of ACTH)**
- **Insulin is administered to produce hypoglycaemia (BGL < 2.2 mmol/L)**
- **Normal response :GH > 20 mU/L and cortisol > 550 mmol/L**

2) *TRH test:*

- **For hypopituitarism, hypothalamic diseases, and less frequently thyroid gland.**
- **IV TRH then blood sampling is at 0, 20, 60 min.**
- **Normal response is a rapid increase in both TSH and prolactin.**

3) *GnRH test:*

- **For hypogonadism**
- **It measures the ability of anterior pituitary to produce FSH and LH**
- **In adults, GnRH produces marked rise in LH and a smaller rise in FSH**
- **In children, reverse the FSH response is greater than LH.**

4) *OGTLwith GH measurement:*

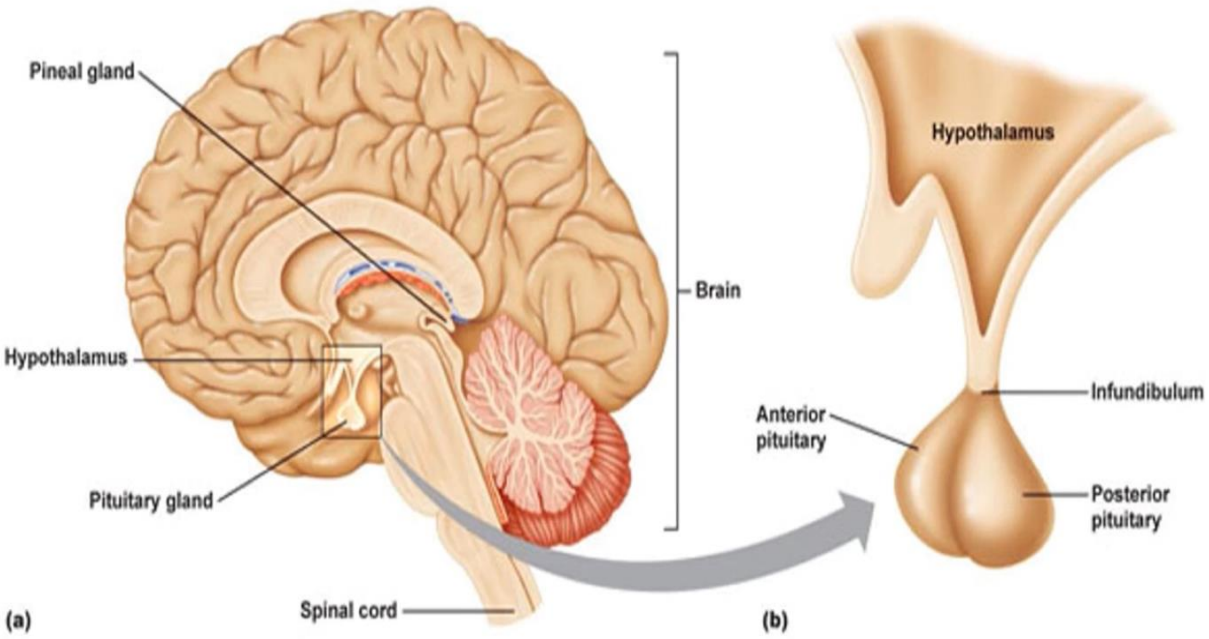
- **Hyperglycaemia suppresses GH secretion**
- **Normal adult OGTT suppresses GH to < 2 m U/L**
- **Acromegalic patient do not response**

5) *Synacthen (ACTH)test:* for adrenal hypo function

- **Short Synacthen Test (SST)**
- **Long Synavthen Test (LST) when the response to SST is equivocal**

6) *Dexamethasone suppression test (DST):*for adrenal hyper function

- **Dexamethasone is an exogenous steroid mimics the negative feedback of endogenous glucocorticoids**
- **For assessment of over-activity of hypothalamic-pituitary adrenal axis**
- **Low dose DST (1 mg Dexamethason orally at 23.00 and cortisol measured at 9.00, if < 50 nmol/L normal)**
- **High dose DST: (8 mg of Dexamethason is used if failure to response to Low dose DST due to overproduction of ACTH (Cushing or ectopic malignant or adrenal production of cortisol)**



Pituitary Gland Disorders

1) *Prolactin (PRL)*

- **Hyperprolactinemia:**
  - **It is a common cause of infertility in both sexes (male and female).**
  - **Symptoms: amenorrhoea and galactorrhoea in female. No signs in male**
  - **Causes:**

    a) Secondary: stress, drugs (estrogens, α-methyl-dopa); primary hypothyroidism (prolactin is stimulated by increased TRH).

    b) Primary: if the secondary causes are excluded. The differential diagnosis is:

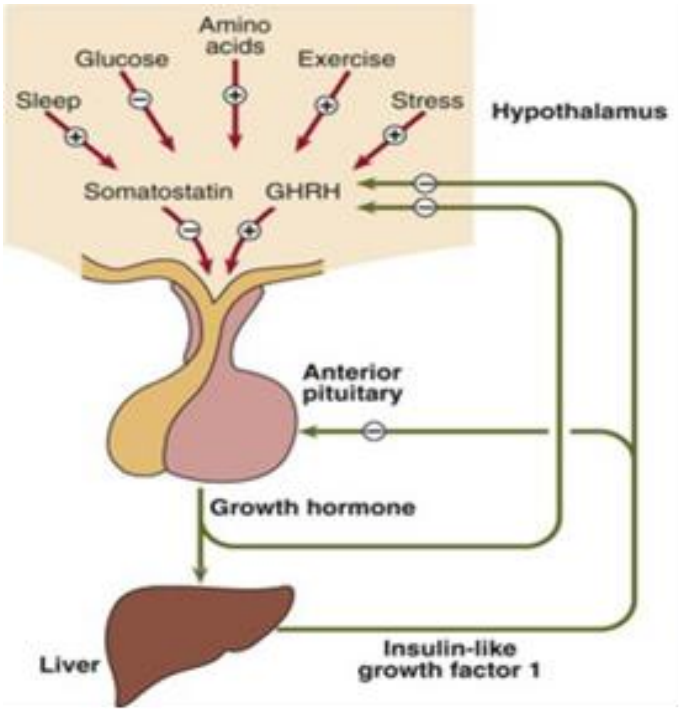
    a) Prolactinoma (Prolactin-secreting pituitary tumour)

    b) Idiopathic hyper secretion (may be due to ↓ dopamine secretion)

  - **Dynamic prolactin test: administration of TRH or metoclopramide, if ↑ prolactin**

    → Idiopathic, if no change in prolactin → Prolactinoma

2) Growth hormone



- **Normal growth in children can be divided into 3 stages:**

1) Rapid growth: first 2 years the rate is affected by embryo period

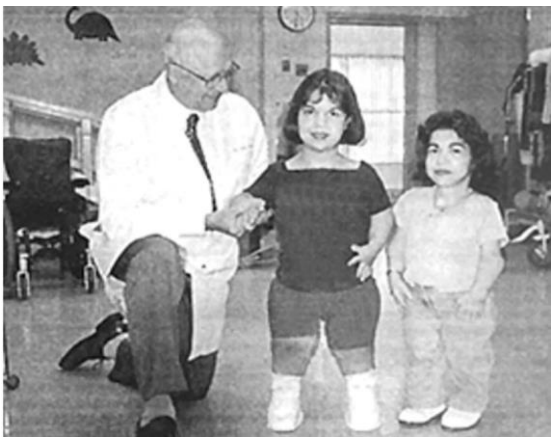
2) Steady growth :next 9 years controlled by GH

3) Puberty growth: controlled by the sex hormone + GH

➢ *Normal regulation of GH(disorders)*

1) *GH insufficiency: Dwarfism* (fail to grow and be short in stature)

- ***Lab diagnosis:*** **To prove the deficiency of GH, patient must fail to respond to two different stimulation tests**



1. **Injection of exogenous insulin to induce severs hypoglycemia, which in turn stimulate secretion of GH. This test is dangerous due to severity of the induced hypoglycemia.**
2. **Injection of CRH to stimulate GH secretion. This taste is safer as it is not inducing hypoglycemia.**
3. **Another test to increase GH involves strenuous exercise. The patient is asked to exercise for 20 min, and then a blood specimen is drawn immediately and assayed for GH level**
4. **Sleep: rise of GH during sleep exclude GH deficiency**
5. **Urinary GH measurement may be used**

- **Treatment : GH replacement therapy**

2) *GH Excess :*

- **Gigantism (childhood): excessive production of GH (due to GH secreting pituitary tumor) before the fusion of epiphyseal plates of bones, where there is accelerated growth of the long bones.**
- **Acromegaly (adulthood): excessive production of GH after the fusion of epiphyseal plates and the cessation of long bones growth. It is marked by enlargement of the bones of the extremities, face and jaw**

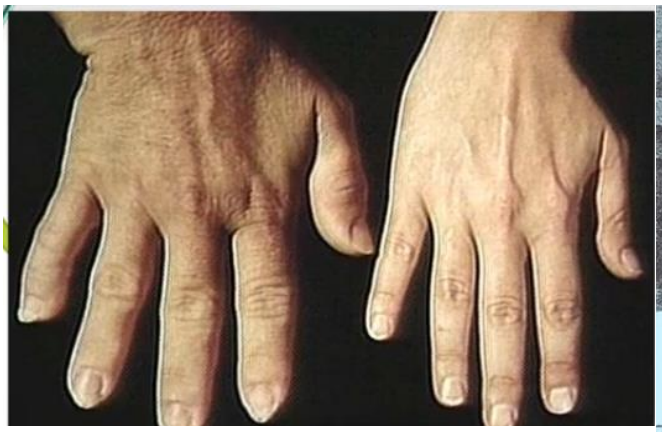
- **Lab. diagnosis**

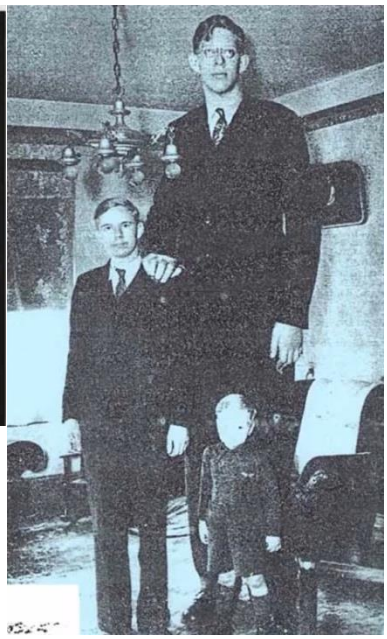
1) OGT suppression test: acromegaly does not response to the hyperglycaemia

2) Serial measurements of GH. Acromegaly, plasma level is 50 ng /ml (normal adult level is 1-5 ng/ml).
3) Increased level of IGF-1 is diagnostic (IGF-1 is produced in response to GH)

- Treatment

1. Surgery
2. Radiation
3. Dopamine agonist: bromocriptine
4. Somatostatins: octreotide





3) *Antidiuretic hormone or APV*

- Diabetes Insipidus (DI) is caused by
  a) Deficiency of ADH (Neurogenic DI)
  b) Failure of kidney to respond to ADH (Nephrogenic DI).
- Symptoms; polyuria (production of large amount of urine about 20 L/day), fatigue, severe dehydration, hypothermia and polydipsia (increased thirst).
- In neurogenic Dl, the cause of the ADH deficiency may be pituitary tumour, traumatic injury, surgical injury or genetic autoimmune.
- In nepherogenic DI, may be due to chronic renal diseases such as chronic pyelonephritis, protein starvation, hypokalaemia, sickle cell anaemia, multiple myeloma, and congenital defects in the receptors in the kidney or defects in the structure of kidney tubules.
- Lab diagnosis
  1) The most valuable test for diagnosis of Dl is urine and plasma osmolality
  2) The plasma level of ADH can be determined
  3) Stimulation test, exogenous ADH is given to the patient to test their response;
- Normal patients respond by decreasing their urine output and increasing urine osmolality.
- Nephrogenic Dl patients will show no response.
- Neurogenic DI patients show increase > 10% in their urine osmolality.